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Functionalized heterocyclics as potential therapeutics

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FUNCTIONALIZED HETEROCYCLICS AS POTENTIAL THERAPEUTICS

by

Anupama Indukuri

A Thesis

Submitted to the
Department of Chemistry & Biochemistry
College of Science & Mathematics
In partial fulfillment of the requirement
For the degree of
Master of Science in Pharmaceutical Sciences
at
Rowan University
June 12, 2019

Thesis Chair: Subash C. Jonnalagadda, Ph.D.
Dedication

This thesis is dedicated to my beloved family. Your patience and encouragement influenced me to undertake higher studies and face the eventualities of life with zeal and enthusiasm. Thank you for your support along the way and in the years to come.
Acknowledgments

I owe my deepest gratitude to Prof. Subash Jonnalagadda for imparting his knowledge and expertise during this research. I thank Dr. Suman Pathi for his guidance in the lab. I am grateful to all my friends who were a constant source of support during my research and beyond.
Abstract

Anupama Indukuri
FUNCTIONALIZED HETEROCYCLICS AS POTENTIAL THERAPEUTICS
2018-2019
Subash Jonnalagadda, Ph.D.
Master of Science in Pharmaceutical Sciences

Heterocyclic compounds play an important role in pharmaceutical drug development. Several natural products and biologically active compounds contain heterocyclic motifs in them. Multicomponent coupling reactions offer an excellent platform for the synthesis of diverse libraries of heterocyclic compounds. We have been working on the synthesis of novel heterocyclic small molecules utilizing reactions such as Baylis-Hillman reaction, Passerini reaction, Click reaction, reductive amination aldol condensation, etc.

In the current project, we prepared three series of heterocyclic compounds using Passerini and Baylis-Hillman reactions as key steps. Owing to the importance of heterocyclic chemistry in drug discovery and the ease of synthesis, the current work would be of interest to medicinal and natural product chemists.
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Chapter 1

Preparation of Heterocyclic Compounds

Introduction

Heterocyclic moieties are present in many natural products and medicinally important compounds.\textsuperscript{1-8} Heterocyclic compounds exhibit wide variety of biological activities such as anti-cancer,\textsuperscript{9} anti-bacterial,\textsuperscript{10-13} anti-fungal,\textsuperscript{14} anti-tuberculosis,\textsuperscript{15} anti-malarial,\textsuperscript{16} anti-asthma,\textsuperscript{17} and other activities.\textsuperscript{18-22} Several drugs also contain heterocyclic motifs in them (eg. Fezolamin,\textsuperscript{23} Celecoxib,\textsuperscript{24} Rimonabant,\textsuperscript{25} Ruxolitinib,\textsuperscript{26} Pyrazofurin,\textsuperscript{27} Crizotinib,\textsuperscript{28} Tepoxalin\textsuperscript{29} Ionazolac\textsuperscript{30}, etc.).\textsuperscript{31-33} We have been working on the development of novel heterocyclic compounds for the past several years.\textsuperscript{34-46} Multicomponent coupling reactions play an important role not only in medicinal chemistry but in organic synthesis as well particularly in the preparation of heterocyclic compounds.\textsuperscript{47} We have also been working on the synthesis of diverse library of compounds via multicomponent coupling reactions. Some of the famous multicomponent coupling reactions include Passerini reaction,\textsuperscript{48-52} Ugi reaction,\textsuperscript{53} Baylis-Hillman reaction,\textsuperscript{54-61} aldol condensation, reductive amination, Click reaction,\textsuperscript{62-65} etc. The two key reactions involved in the present study include Passerini reaction (Figure 1) and Baylis-Hillman reaction (Figure 2).
Passerini Reaction

Passerini reaction involves the synthesis of α-acyloxy carboxamides 4 via a three-component coupling reaction between aldehyde/ketones 1, carboxylic acids 2, and isocyanides 3, while Ugi reaction involves a four-component coupling of aldehydes/ketones 1, carboxylic acids 2, isocyanides 3, and amines 5 towards the synthesis of α-acylamino amides 6 (Figure 1).

\[
\begin{align*}
&\text{Passerini} \\
1 & \quad \text{acrylates, vinyl ketones, and acrolein} \quad 8 \quad \text{with aldehydes} \quad 7 \quad \text{to produce densely functionalized} \\
&\text{allylic alcohols} \quad 9 \quad \text{in high yields (Figure 2).}^{66} \text{While this reaction does tolerate wide variety} \\
&\text{of functional groups, it does have a drawback of being extremely slow (often this reaction}
\end{align*}
\]
takes two weeks or longer for completion) and multiple efforts have been made accordingly towards increasing the rate of this reaction. Baylis-Hillman reaction has been reported with olefins such as acrylate, vinyl ketone, acrolein, acrylamide, acrylonitrile, vinyl sulfone, vinyl sulfoxide, vinyl phosphonate, and allenyl esters leading to the formation of corresponding allylic alcohols. These allylic alcohols can be further functionalized via acetylation followed by nucleophilic substitution to generate diverse library of compounds (Figure 2).

\[ \text{Figure 2. Baylis-Hillman Reaction} \]
Proposed Target Compounds

Based on our interest involving the applications of heterocyclic chemistry in medicinal compounds, we undertook the synthesis of conjugates 12-14 using Baylis-Hillman and Passerini reactions as key steps (Figure 3).

*Figure 3. Target Compounds*
**Proposed Synthesis of Target 12**

We hypothesized the synthesis of 12 via Passerini reaction of bromomethyl benzoic acid 15 with isocyanide 16, and benzaldehyde 17 followed by sequential nucleophilic substitution with piperazine as shown in Figure 4.
Proposed Synthesis of Target 13

The synthesis of conjugate 13 was envisioned via conversion of amine 22 into isocyanate 23 followed by reaction with monoprotected ethylenediamine 24 and amide coupling with Baylis-Hillman reaction derived α-piperazinylmethylcinnamic acid 27. The synthesis of compound 27 was in turn hypothesized via substitution of BH acetate 21 with N-methylpiperazine 26 (Figure 5).

Figure 5. Proposed Synthesis of Target Compound 13
Proposed Synthesis of Target 14

The synthesis of 14 was proposed via sequential coupling of glycine analog 28 with aniline 22 and α-piperazinylmethylcinnamic acid 27 (Figure 6).

Figure 6. Proposed Synthesis of Target Compound 14
Preparation of Target Compound 12

The synthesis of compound 12 was initiated with the Passerini reaction of \( p \)-bromomethylbenzoic acid 15. 15 was in turn was synthesized via benzylic halogenation of \( p \)-toluic acid using potassium bromate and sodium thiosulfate.\(^{86}\) \( p \)-Bromomethylbenzoic acid 15 was further reacted with \( t \)-butyl isocyanide and three aldehydes (benzaldehyde, \( p \)-fluorobenzaldehyde, and \( p \)-cyanobenzaldehyde) 17a-c in water and stirred at room temperature overnight to obtain the α-acyloxy amides 18a-c in very good yield (Figure 7). The compounds synthesized via Passerini reaction are shown in Figure 8.

![Chemical Reaction](image_url)

*Figure 7. Preparation of 18a-c via Passerini Reaction*
The α-acyloxyamides 18a-c obtained via Passerini reaction were further reacted with N-Boc piperazine 19 in the presence of potassium carbonate and DMF to obtain N-Boc piperazinylmethyl benzoates 30a-c (Figure 9). The compounds synthesized via this protocol are shown in Figure 10.
The Boc protecting group in 30a-c was cleaved via treatment with hydrochloric acid in dioxane to obtain the piperazine analogs 20a-c (Figure 11). The compounds synthesized via this protocol are shown in Figure 12.
The acetates 21a-d required for coupling with piperazines 20a-c were prepared via Baylis-Hillman reaction. Treatment of methyl acrylate 32 with benzaldehyde, p-fluorobenzaldehyde, p-cyanobenzaldehyde, and p-anisaldehyde 31a-d in the presence of diazabicyclo[2.2.2]octane yielded the allylic alcohols 33a-d, which were further subjected to acetylation with acetic anhydride and triethyl amine to yield the requisites acetates 21a-d (Figure 13). The acetates prepared via this protocol are shown in Figure 14.
The target compounds 12a-f were eventually synthesized via the reaction of piperazine hydrochloride 20a-c with acetates 21a-d in the presence of potassium carbonate and DMF (Figure 15). The target compounds synthesized via this protocol (Figure 16) were rigorously characterized using proton and carbon NMR spectroscopy as well as mass spectrometry.
Figure 15. Preparation of Target Compounds 12a-f
Preparation of Target Compound 13

The synthesis of target compound 13 was initiated with the preparation of ureas 25a-c (Figure 17). Isocyanates 23a-c were obtained upon treatment of aniline, 4-cyano-3-trifloromethylaniline, and 4-nitro-3-trifloromethylaniline (22a-c) with triphosgene. The isocyanates 23a-c were further treated with N-boc-ethylenediamine 24 in the presence of triethylamine to afford the ureas 34a-c, which were further deprotected via acid treatment yielding the amine hydrochlorides 25a-c (Figure 17). The compounds synthesized via this protocol are shown in Figure 18.
Figure 17. Preparation of N-Phenyl-N’-2-aminoethyl ureas 25a-c

Figure 18. N-Phenyl-N’-2-aminoethyl ureas 25a-c
Final target compounds 13a-c were synthesized via EDCI-HOBt coupling of amine hydrochlorides 25a-c with Baylis-Hillman reaction derived α-piperazinylmethylcinnamic acid 27. The cinnamic acid 27 was synthesized in two steps from Baylis-Hillman acetate 21 via nucleophilic substitution with N-methylpiperazine 26 followed by alkaline hydrolysis of the resulting α-piperazinylmethylcinnamate 35 (Figure 19). The target compounds synthesized via this protocol are shown in Figure 20. The two compounds 13b and 13c were inspired from the chemotherapeutic drugs such as nilutamide and bicalutamide.
Figure 19. Preparation of Target Compounds 13
Preparation of Target Compound 14

Finally, the target compounds 14a-b were synthesized starting from N-Boc glycine 28. Coupling of 28 with amines 22a-b in the presence of oxalyl chloride and triethyl amine resulted in the formation of amides 36a-b, which were further deprotected using HCl and dioxane to yield the amine hydrochlorides 29a-b. The N-methylpiperazinylmethyl cinnamic acid 27 synthesized above (Figure 19) was used for reaction with amine hydrochlorides 29a-b under EDCI and HOBT coupling conditions to generate the final target compounds 14a-b (Figure 21). The compounds synthesized via this protocol are shown in Figure 22. The biological evaluation of these compounds as potential anti-cancer agents is underway.
Figure 21. Preparation of Target Compounds 14

![Reaction Scheme](image)

Figure 22. Target Compounds 14 Synthesized via Peptide Coupling

![Compounds 14a and 14b](image)
Conclusions

Heterocyclic compounds play an important role in medicinal chemistry and drug discovery. In this project, we have prepared three series of heterocyclic compounds using Passerini and Baylis-Hillman reactions as key steps. Once the preliminary biological screening has been completed, the ease of synthesis of the above-mentioned protocols coupled with the versatility of the multicomponent coupling reactions, will enable us to synthesize diverse library of compounds for potential drug-design applications.
Chapter 2

Experimental Procedures and Spectral Characterization

Materials

All the reactants were of reagent grade, and purchased from Acros Organics, Alfa Aesar or Sigma Aldrich, and used without further purification. All solvents were used without further drying or purification and were of ACS grade purchased from Fisher Scientific.

Instrumentation

Nuclear Magnetic Spectroscopy (NMR) spectra were produced using the Varian 400 MHz spectrophotometer. The instrument was maintained at 25° C operating at 400 MHz for $^1$H NMR, and 100 MHz for $^{13}$C NMR. The deuterated solvent (CDCl$_3$, DMSO-d$_6$) used for each respective spectrum is referenced to the appropriate literature peak shift.

Procedures

Preparation of 2-(tert-Butylamino)-2-oxo-1-phenylethyl 4-(bromomethyl)benzoate 18a:

To a stirred solution of benzaldehyde 17a (500 mg, 4.7 mmol) and 4-
(bromomethyl)benzoic acid 15 (1.2 g, 5.6 mmol) in water (5.0 mL), was added tert-butyl isocyanide (469 mg, 5.6 mmol) and stirred overnight at room temperature. Upon completion as indicated by thin layer chromatography (TLC), the reaction mixture was washed with saturated NaHCO₃ followed by extraction with ethyl acetate (2 x 10 mL), dried over anhydrous Na₂SO₄ and concentrated under vacuum. The resulting residue was purified by triturating with hexanes to obtain pure 1.7 g (92%) of 18a as white solid. Mp 155 – 157 ºC; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.06 (d, J = 8.4 Hz, 2H), 7.47 – 7.54 (m, 4H), 7.35 – 7.42 (m, 3H), 6.20 (s, 1H), 5.92 (s, 1H), 4.50 (s, 2H), 1.36 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 167.3, 164.4, 143.4, 135.8, 130.3, 129.3, 129.2, 128.9, 128.8, 127.5, 76.2, 51.6, 32.1, 28.7. ESIMS: m/z calculated for C₂₀H₂₂BrNO₃ (M+H)⁺ 404.09, found 404.02.

Preparation of 2-(tert-Butylamino)-1-(4-fluorophenyl)-2-oxoethyl 4-(bromomethyl)benzoate 18b: Procedure similar to that of 18a. The reaction of 4-fluoro benzaldehyde 17b (400 mg, 3.2 mmol), 4-(bromomethyl)benzoic acid 15 (832 mg, 3.86 mmol), and tert-butyl isocyanide (320 mg, 3.86 mmol) yielded 1.2 g (89%) of 18b as white solid. Mp 167 – 169 ºC; ¹H NMR (400 MHz CDCl₃): δ (ppm) 8.04 (d, J = 8.4 Hz, 2H), 7.45 – 7.53 (m, 4H), 7.07 (t, J = 8.7 Hz, 2H), 6.18 (s, 1H), 5.98 (s, 1H), 4.50 (s, 2H), 1.37
\( \delta (\text{ppm}) 167.1, 164.3, 162.9 (d, J = 248.0 \text{ Hz}), 143.5, \\
131.7 (d, J = 3.3 \text{ Hz}), 130.2, 129.4 (d, J = 8.5 \text{ Hz}), 129.3, 129.1, 115.8 (d, J = 21.8 \text{ Hz}), \\
75.4, 51.7, 31.9, 28.7. \text{ESIMS: m/z calculated for } C_{20}H_{21}BrFNO_3 (M+Na)^+ 444.06, \text{found 444.05.}

\[ \text{Preparation of } 2-(\text{tert-Butylamino})-1-(4-cyanophenyl)-2-\text{oxoethyl } 4-(\text{bromomethyl})\text{benzoate } 18c: \text{Procedure similar to that of } 18a. \text{The reaction of 4-cyano benzaldehyde } 17c (500 \text{ mg, 3.8 mmol}), 4-(\text{bromomethyl})\text{benzoic acid } 15 (984 \text{ mg, 4.6 mmol}), \text{and } \text{t}^\prime\text{butyl isocyanide (379 mg, 4.6 mmol) yielded 1.4 g (86\%) of } 18c \text{ as white solid. Mp 161 – 164 }^\circ\text{C; } \text{H NMR (400 MHz, CDCl}_3\text{); } \delta (\text{ppm}) 8.05 (d, J = 8.4 \text{ Hz, 2H}), \\
7.68 (d, J = 8.4 \text{ Hz, 2H}), 7.63 (d, J = 8.4 \text{ Hz, 2H}), 7.52 (d, J = 8.0 \text{ Hz, 2H}), 6.22 (s, 1H), \\
6.07 (s, 1H), 4.51 (s, 2H), 1.36 (s, 9H); \text{C NMR (101 MHz, CDCl}_3\text{); } \delta (\text{ppm}) 166.1, 164.0, \\
143.9, 140.9, 132.5, 130.2, 129.4, 128.6, 127.9, 118.4, 112.7, 75.2, 51.9, 31.8, 28.6. \text{ESIMS: m/z calculated for } C_{21}H_{21}BrN_2O_3 (M+Na)^+ 451.06, \text{found 451.05.}

\[ \text{Preparation of } \text{tert-Butyl } 4-(4-(2-(\text{tert-butylamino})-2-\text{oxo-1-phenylethoxy)carbonyl}benzyl) \text{piperazine-1-carboxylate } 30a: \text{Potassium carbonate} \]
(513 mg, 3.7 mmol) was added to a stirred solution of tert-butyl piperazine-1-carboxylate (507 mg, 2.7 mmol) and 18a (1.0 g, 2.5 mmol) in N,N-dimethylformamide (10.0 mL) at room temperature and stirred overnight at room temperature. Upon completion, the reaction mixture was diluted with cold water to affect the precipitation of solid. The resulting solid was filtered and dried under vacuum to furnish 1.06 g (84%) of 30a as white solid. Mp 97 – 99 °C; 1H NMR (400 MHz, CDCl3): δ (ppm) 8.03 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 6.8 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.33 – 7.41 (m, 3H), 6.20 (s, 1H), 5.98 (s, 1H), 3.56 (s, 2H), 3.36 – 3.47 (m, 4H), 2.33 – 2.43 (m, 4H), 1.45 (s, 9H), 1.36 (s, 9H); 13C NMR (101 MHz, CDCl3): δ (ppm) 167.4, 164.8, 154.7, 144.3, 135.9, 129.8, 129.1, 128.8, 128.7, 128.2, 127.4, 79.6, 75.9, 62.5, 52.9, 51.5, 43.9, 43.1, 28.7, 28.4; ESIMS: m/z calculated for C29H39N3O5 (M+Na)+ 532.28, found 532.25.

Preparation of tert-Butyl 4-(4-((2-(tert-butylamino)-1-(4-fluorophenyl)-2-oxoethoxy) carbonyl) benzyl) piperazine-1-carboxylate (30b): Procedure similar to that of 30a. The reaction of 18b (1.0 g, 2.4 mmol) with tert-butyl piperazine-1-carboxylate (484 mg, 2.6 mmol) in presence of potassium carbonate (488 mg, 3.5 mmol) yielded 1.0 g (82%) of 30b as white solid. Mp 127 – 129 °C; 1H NMR (400 MHz, CDCl3): δ (ppm) 8.01 (d, J = 8.0 Hz, 2H), 7.49 (dd, J = 5.2, 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.07 (t, J = 8.6 Hz, 2H), 6.18 (s, 1H), 6.03 (s, 1H), 3.56 (s, 2H), 3.42 (t, J = 4.6 Hz, 4H), 2.38 (t, J = 4.6 Hz, 4H),
1.45 (s, 9H), 1.37 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ (ppm) 167.2, 164.7, 162.9 (d, $J$ = 247.8 Hz), 154.7, 144.5, 131.9 (d, $J$ = 3.1 Hz), 129.8, 129.3 (d, $J$ = 8.4 Hz), 129.1, 128.1, 115.7 (d, $J$ = 21.7 Hz), 79.6, 75.2, 62.5, 52.9, 51.6, 43.9, 43.2, 28.6, 28.4; ESIMS: m/z calculated for C$_{29}$H$_{38}$FN$_3$O$_5$ (M+Na)$^+$ 550.27, found 550.35.

**Preparation of tert-Butyl 4-((4-(2-(tert-butylamino)-1-(4-cyanophenyl)oxy)carbonyl)benzyl)piperazine-1-carboxylate ( ):** Procedure similar to that of 30a. The reaction of 18c (900 mg, 2.1 mmol) with tert-butyl piperazine-1-carboxylate (429 mg, 2.3 mmol) in presence of potassium carbonate (432 mg, 3.1 mmol) yielded 883 mg (79%) of 30c as white solid. Mp 158 – 160 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 8.02 (d, $J$ = 8.0 Hz, 2H), 7.68 (d, $J$ = 8.4 Hz, 2H), 7.63 (d, $J$ = 8.4 Hz, 2H), 7.47 (d, $J$ = 8.0 Hz, 2H), 6.23 (s, 1H), 6.13 (s, 1H), 3.58 (s, 2H), 3.43 (t, $J$ = 4.6 Hz, 4H), 2.39 (t, $J$ = 4.6 Hz, 4H), 1.45 (s, 9H), 1.37 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ (ppm) 166.3, 164.4, 154.7, 144.9, 141.1, 132.4, 129.8, 129.2, 127.8, 127.6, 118.4, 112.5, 79.7, 74.9, 62.5, 52.9, 51.8, 43.9, 43.0, 28.6, 28.4; ESIMS: m/z calculated for C$_{30}$H$_{38}$N$_4$O$_5$ (M+H)$^+$ 557.27, found 557.36.
**Preparation of 2-(tert-Butylamino)-2-oxo-1-phenylethyl-4-((4-(2-(methoxycarbonyl)-3-phenylallyl)piperazin-1-yl)methyl)benzoate 12a:** To a stirred solution of acrylate 21a (150 mg, 0.64 mmol) in N,N-dimethylformamide (10.0 mL), was added compound 20a (313 mg, 0.7 mmol) and followed by addition of K₂CO₃ (132 mg, 0.96 mmol). The reaction was stirred for 10 h and diluted with cold water upon completion. The reaction mixture was extracted with ethyl acetate (2 x 10 mL) and the combined extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Further purification of the crude product by chromatography (silica gel, hexanes: ethyl acetate, 4:1) yielded 12a as white solid (291 mg, 78%). Mp 124 – 126 °C; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.03 (d, J = 8.4 Hz, 2H), 7.85 (s, 1H), 7.63 – 7.66 (m, 2H), 7.51 (dd, J = 1.5, 7.8 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.29 – 7.39 (m, 6H), 6.21 (s, 1H), 6.02 (s, 1H), 3.81 (s, 3H), 3.54 (s, 2H), 3.36 (s, 2H), 2.37 – 2.58 (m, 8H), 1.37 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 169.3, 167.7, 165.0, 145.1, 143.6, 136.3, 135.6, 130.7, 129.9, 129.4, 129.2, 129.0, 128.9, 128.6, 128.3, 127.6, 76.2, 62.8, 53.5, 53.4 (2C), 52.8, 52.3, 51.8, 28.9; ESIMS: m/z calculated for C₃₅H₄₁N₅O₅ (M+H)⁺ 584.3, found 584.4, HPLC purity 94.2%. 

![Chemical Structure](image-url)
Preparation of 2-((tert-butylamino)-2-oxo-1-phenylethyl)-4-((4-(3-(4-fluorophenyl)-2-methoxycarbonyl)allyl)piperazin-1-yl)methyl)benzoate 12b: Procedure similar to that of 12a. The reaction of 21b (150 mg, 0.59 mmol) with compound 20a (292 mg, 0.65 mmol) in presence of potassium carbonate (123 mg, 0.88 mmol) yielded 266 mg (75%) of 12b as white solid. Mp 98 – 101 °C; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.02 (d, J = 8.0 Hz, 2H), 7.81 (s, 1H), 7.70 (dd, J = 5.6, 8.8 Hz, 2H), 7.51 (dd, J = 1.8, 7.8 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.33 – 7.39 (m, 3H), 7.07 (t, J = 8.4 Hz, 2H), 6.21 (s, 1H), 6.00 (s, 1H), 3.80 (s, 3H), 3.55 (s, 2H), 3.33 (s, 2H), 2.36 – 2.60 (m, 8H), 1.36 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 169.2, 167.6, 165.0, 163.27 (d, J = 250.3 Hz), 145.0, 142.8, 136.2, 132.94 (d, J = 8.1 Hz), 131.76 (d, J = 3.2 Hz), 129.9, 129.3, 129.1, 128.9, 128.3, 127.6, 115.63 (d, J = 21.5 Hz), 76.1, 62.7, 53.5, 53.4 (2C), 52.7, 52.4, 52.3, 51.8, 28.9; ESIMS: m/z calculated for C₃₅H₄₆FN₃O₅ (M+H)+ 602.3, found 602.4; HPLC purity 89.2%.
Preparation of 2-(tert-butylamino)-2-oxo-1-phenylethyl-4-((4-(2-(methoxycarbonyl)-3-(4-methoxyphenyl)allyl)piperazin-1-yl)methyl)benzoate 12c: Procedure similar to that of 12a. The reaction of 21d (150 mg, 0.56 mmol) with compound 20a (275 mg, 0.61 mmol) in presence of potassium carbonate (116 mg, 0.84 mmol) yielded 254 mg (74%) of X as white solid. Mp 95 – 98 °C; \(^1^H\) NMR (400 MHz, CDCl\(_3\)): δ (ppm) 7.94 (d, \(J = 8.0\) Hz, 2H), 7.74 (s, 1H), 7.59 (d, \(J = 8.4\) Hz, 2H), 7.43 (d, \(J = 6.8\) Hz, 2H), 7.35 (d, \(J = 8.0\) Hz, 2H), 7.23 – 7.32 (m, 3H), 6.82 (d, \(J = 8.8\) Hz, 2H), 6.13 (s, 1H), 6.01 (s, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.46 (s, 2H), 3.27 (s, 2H), 2.26 – 2.56 (m, 8H), 1.27 (s, 9H); \(^1^C\) NMR (101 MHz, CDCl\(_3\)): δ (ppm) 169.5, 167.7, 165.0, 160.6, 145.1, 143.8, 136.3, 132.9, 129.9, 129.4, 129.0, 128.9 (2C), 128.3, 127.6, 127.2, 114.1, 76.2, 62.7, 55.5, 53.6, 53.4, 53.3, 52.7, 52.2, 52.2, 51.8, 28.9; ESIMS: m/z calculated for C\(_{36}\)H\(_{43}\)N\(_3\)O\(_6\) (M+H\(^+\)) 614.3, found 614.4; HPLC purity 90.2%. 

![Chemical structure image]
Preparation of 2-(tert-Butylamino)-1-(4-cyanophenyl)-2-oxoethyl-4-((4-(3-(4-fluorophenyl)-2-(methoxy carbonyl)allyl)piperazin-1-yl)methyl)benzoate 12d: Procedure similar to that of 12a. The reaction of 21b (150 mg, 0.59 mmol) with compound 20c (308 mg, 0.65 mmol) in presence of potassium carbonate (122 mg, 0.88 mmol) yielded 292 mg (79%) of X as white solid. Mp 86 – 88 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 8.01 (d, $J = 8.4$ Hz, 2H), 7.82 (s, 1H), 7.60 – 7.74 (m, 6H), 7.47 (d, $J = 8.4$ Hz, 2H), 7.07 (t, $J = 8.6$ Hz, 2H), 6.24 (s, 1H), 6.13 (s, 1H), 3.81 (s, 3H), 3.57 (s, 2H), 3.33 (s, 2H), 2.39 – 2.58 (m, 8H), 1.37 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ (ppm) 169.2, 166.5, 164.6, 163.3 (d, $J = 250.4$ Hz), 145.6, 142.8, 141.3, 132.9 (d, $J = 8.2$ Hz), 132.7, 131.7 (d, $J = 3.2$ Hz), 129.9, 129.5, 129.3, 128.1, 127.6, 118.7, 115.6 (d, $J = 21.4$ Hz), 112.8, 75.2, 62.7, 53.5, 53.4, 52.7, 52.4, 52.1, 28.9; ESIMS: m/z calculated for C$_{36}$H$_{39}$FN$_4$O$_5$ (M+H)$^+$ 627.3, found 627.4; HPLC purity 91.3%.
Preparation of 2-(tert-Butylamino)-1-(4-cyanophenyl)-2-oxoethyl-4-((4-(3-(4-cyanophenyl)-2-(methoxy carbonyl)allyl)piperazin-1-yl)methyl)benzoate 12e: Procedure similar to that of 12a. The reaction of 21c (150 mg, 0.57 mmol) with compound 20c (295 mg, 0.62 mmol) in presence of potassium carbonate (118 mg, 0.86 mmol) yielded 274 mg (76%) of 12e as cream color solid. Mp 89 – 92 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 8.01 (d, $J = 8.4$ Hz, 2H), 7.77 – 7.82 (m, 3H), 7.62 – 7.69 (m, 6H), 7.46 (d, $J = 8.4$ Hz, 2H), 6.23 (s, 1H), 6.12 (s, 1H), 3.83 (s, 3H), 3.56 (s, 2H), 3.31 (s, 2H), 2.36 – 2.57 (m, 8H), 1.37 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ (ppm) 168.6, 166.5, 164.6, 145.5, 141.4, 141.3, 140.1, 132.7, 132.7, 132.2, 131.1, 129.9, 129.5, 128.9, 128.1, 127.7, 118.8, 118.6, 112.8, 112.4, 75.2, 62.6, 53.4, 53.4, 52.7, 52.6, 52.1, 28.9; ESIMS: m/z calculated for C$_{37}$H$_{39}$N$_5$O$_5$ (M+H)$^+$ 634.3, found 634.4; HPLC purity 96.2%.
Preparation of 2-(tert-Butylamino)-1-(4-fluorophenyl)-2-oxoethyl-4-((4-(3-(4-
fluorophenyl)-2-(methoxy carbonyl)allyl)piperazin-1-yl)methyl)benzoate 12f: Procedure
similar to that of 21a. The reaction of 21b (150 mg, 0.59 mmol) with compound 20b (301
mg, 0.65 mmol) in presence of potassium carbonate (122 mg, 0.88 mmol) yielded 296 mg
(81%) of 12f as white solid. Mp 94 – 96 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.93 (d,
J = 7.9 Hz, 2H), 7.73 (s, 1H), 7.62 (dd, J = 5.7, 7.8 Hz, 2H), 7.42 (dd, J = 5.7, 8.0 Hz, 2H),
7.36 (d, J = 7.8 Hz, 2H), 6.97 (t, J = 8.5 Hz, 4H), 6.11 (s, 1H), 6.07 (s, 1H), 3.71 (s, 3H),
3.46 (s, 2H), 3.24 (s, 2H), 2.24 – 2.55 (m, 8H), 1.28 (s, 9H); ¹³C NMR (101 MHz, CDCl₃):
δ (ppm) 169.2, 167.4, 164.9, 163.3 (d, J = 250.2 Hz), 163.2 (d, J = 247.8 Hz), 145.2, 142.8,
132.9 (d, J = 8.2 Hz), 132.2 (d, J = 3.3 Hz), 131.8 (d, J = 3.3 Hz), 129.9, 129.6 (d, J = 8.4
Hz), 129.4, 129.4, 128.1, 115.9 (d, J = 21.7 Hz), 115.6 (d, J = 21.5 Hz), 75.4, 62.7, 53.5,
53.4, 52.7, 52.4, 51.9, 28.9; ESIMS: m/z calculated for C₃₅H₃₉F₂N₃O₅ (M+H)+ 620.3, found
620.4; HPLC purity 96.5%. 

31
Preparation of 2-(3-(4-cyano-3-(trifluoromethyl)phenyl)ureido)ethan-1-aminiumchloride

25b: Procedure similar to that of 25a-c. Yield: 85%; pale cream solid; mp 233 – 236 °C; 
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 10.44 (s, 1H), 8.18 (d, \(J = 2.0\) Hz, 1H), 8.03 (br s, 3H), 7.95 (d, \(J = 8.6\) Hz, 1H), 7.73 (dd, \(J = 2.0, 8.6\) Hz, 1H), 7.06 (t, \(J = 5.8\) Hz, 1H), 3.30 – 3.38 (m, 2H), 2.82 – 2.92 (m, 2H); \(^1^3\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) (ppm) 155.5, 145.8, 136.6, 132.1 (q, \(J = 31.3\) Hz), 123.0 (q, \(J = 273.6\) Hz), 120.5, 116.6, 115.0 (q, \(J = 4.7\) Hz), 99.18 (q, \(J = 2.9\) Hz), 37.5, 36.9; ESIMS: m/z calculated for C\(_{11}\)H\(_{12}\)Cl\(_3\)F\(_3\)N\(_4\)O (M)\(^+\) 273.10, found 272.95;

Preparation of 2-(3-(4-nitro-3-(trifluoromethyl)phenyl)ureido)ethan-1-aminiumchloride

25c: Procedure similar to that of 25a-c. Yield: 87%; pale cream solid; mp 220 – 224 °C; 
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 10.34 – 10.45 (m, 1H), 8.21 (d, \(J = 2.3\) Hz, 1H), 8.12 (d, \(J = 9.0\) Hz, 1H), 7.96 (br s, 3H), 7.77 (dd, \(J = 2.2, 9.0\) Hz, 1H), 6.99 – 7.06 (m, 1H), 3.35 (q, \(J = 6.0\) Hz, 2H), 2.83 – 2.94 (m, 2H); \(^1^3\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) (ppm) 155.4, 146.2, 139.7, 128.3, 123.7 (q, \(J = 33.0\) Hz), 122.6 (q, \(J = 262.4\) Hz), 120.4, 115.8 (q, \(J = 6.0\) Hz), 39.4, 37.6; ESIMS: m/z calculated for C\(_{10}\)H\(_{12}\)Cl\(_3\)F\(_3\)N\(_3\)O (M)\(^+\) 293.09, found 293.00.
Preparation of (E)-2-((4-methylpiperazin-1-yl)methyl)-3-phenyl-N-(2-(3-phenylureido)ethyl) acrylamide 13a: The reaction of acid 27 (150 mg, 0.58 mmol), with amine 25a (150 mg, 0.70 mmol) yielded 198 mg (81%) of 13a as pale cream solid. Mp 104 – 107 °C; \(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 10.02 (t, \(J = 5.1\) Hz, 1H), 8.04 (s, 1H), 7.88 (s, 1H), 7.37 (d, \(J = 8.1\) Hz, 2H), 7.27 – 7.34 (m, 3H), 7.11 – 7.21 (m, 4H), 6.93 (t, \(J = 7.4\) Hz, 1H), 6.40 (br s, 1H), 3.44 – 3.54 (m, 4H), 3.40 (s, 2H), 2.26 – 2.77 (m, 8H), 2.21 (s, 3H). \(^{13}C\) NMR (101 MHz, CDCl\(_3\)): \(\delta\) (ppm) 169.5, 156.4, 140.5, 139.6, 135.0, 129.7, 128.9, 128.4, 128.2, 122.3, 119.0, 54.9, 54.6, 52.1, 45.6, 39.9, 39.6; ESIMS: m/z calculated for C\(_{24}\)H\(_{31}\)N\(_{5}\)O\(_{2}\) (M+H\(^{+}\)) 422.26, found 422.21; HPLC purity 98.2%.

Preparation of (E)-N-(2-(3-(4-cyano-3-(trifluoromethyl)phenyl)ureido)ethyl)-2-((4-methyl-piperazin-1-yl)methyl)-3-phenylacrylamide 13b: The reaction of acid 27 (130 mg, 0.50 mmol), with amine 25b (185 mg, 0.60 mmol) yielded 196 mg (76%) of 13b as pale cream solid. Mp 119 – 121 °C; \(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm) 10.35 – 10.43 (m, 1H), 9.00 (br s, 1H), 7.89 (s, 1H), 7.84 (s, 1H), 7.68 (d, \(J = 8.1\) Hz, 1H), 7.55 (d, \(J = 8.5\) Hz, 1H), 7.23 – 7.37 (m, 3H), 7.10 – 7.16 (m, 2H), 6.67 (br s, 1H), 3.48 – 3.58 (m, 4H),
3.46 (s, 2H), 2.31 – 2.67 (m, 8H), 2.27 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ (ppm) 170.3, 155.2, 144.5, 141.0, 135.6, 134.4, 133.7 (q, $J = 32.3$ Hz), 129.3, 128.8, 128.7, 128.6, 122.3 (q, $J = 274.1$ Hz), 119.9, 116.1, 115.5 (m), 101.1 (m), 54.9, 54.6, 52.1, 45.7, 39.8, 29.7; ESIMS: m/z calculated for C$_{26}$H$_{29}$F$_3$N$_6$O$_2$ (M+H)$^+$ 515.24, found 515.19; HPLC purity 99.8%.

![Chemical Structure](image)

Preparation of (E)-2-\(((4\text{-methylpiperazin-1-yl})\text{methyl})\text{-N-(2-\((3\text{-}(4\text{-nitro-3\text{-trifluoromethyl})\text{phenyl})\text{ureido})\text{ethyl}\))\text{-3-phenylacrylamide 13c:} The reaction of acid 27 (110 mg, 0.42 mmol), with amine 25c (166 mg, 0.51 mmol), yielded 175 mg (78%) of 13c as pale yellow solid. Mp 128 – 131 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 10.46 (t, $J = 5.1$ Hz, 1H), 9.14 (s, 1H), 7.79 – 7.91 (m, 3H), 7.74 (d, $J = 8.1$ Hz, 1H), 7.28 – 7.36 (m, 3H), 7.10 – 7.15 (m, 2H), 6.71 (br s, 1H), 3.49 – 3.59 (m, 4H), 3.45 (s, 2H), 2.29 – 2.65 (m, 8H), 2.25 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ (ppm) 170.3, 155.2, 144.9, 140.9, 140.6, 134.3, 129.3, 128.8, 128.6, 128.5, 127.4, 125.2 (q, $J = 33.6$ Hz), 121.9 (q, $J = 273.4$ Hz), 119.7, 116.4 (m), 55.0, 54.6, 52.2, 45.8, 39.9, 39.8; ESIMS: m/z calculated for C$_{25}$H$_{29}$F$_3$N$_6$O$_4$ (M+H)$^+$ 535.23, found 535.27; HPLC purity 98.3%.

34
Preparation of (E)-2-((4-methylpiperazin-1-yl)methyl)-N-(2-oxo-2-(phenylamino)ethyl)-3-phenylacrylamide 14a: N,N-diisopropylethylamine (239 µL, 1.38 mmol), HOBt (68 mg, 0.51 mmol), and EDCI (97 mg, 0.51 mmol) were added at 0 °C to a stirred solution of the acid 28 (120 mg, 0.46 mmol), in dichloromethane (10.0 mL) and the reaction was stirred for 30 min. The amine 29 (103 mg, 0.55 mmol), was added in one portion and the reaction was stirred overnight at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was quenched by the addition of saturated NaHCO₃ solution and extracted with dichloromethane (2 x 10.0 mL). The combined extracts were washed with brine (10.0 mL), dried over anhydrous Na₂SO₄, concentrated in vacuo, and purified by column chromatography (silica gel, hexanes:ethyl acetate) to obtain 140 mg (78%) of pure amide 14a as pale cream solid. Mp 115 – 117 °C; ¹H NMR (400 MHz, CDCl₃): δ (ppm) 10.51 (t, J = 5.2 Hz, 1H), 8.94 (s, 1H), 8.00 (s, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.23 – 7.40 (m, 6H), 7.10 (t, J = 7.4 Hz, 1H), 4.20 (d, J = 5.6 Hz, 2H), 3.48 (s, 2H), 2.32 – 2.86 (m, 8H), 2.28 (s, 4H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 169.4, 167.7, 141.1, 138.1, 135.1, 129.2, 129.0, 128.9, 128.4, 128.2, 124.1, 119.8, 54.8, 54.7, 52.3, 45.8, 45.6; ESIMS: m/z calculated for C₂₅H₂₇N₄O₂ (M+H)⁺ 393.23, found 393.31; HPLC purity 96.9%.

![Chemical Structure](image-url)
Preparation of (E)-N-(2-((4-cyano-3-(trifluoromethyl)phenyl)amino)-2-oxoethyl)-2-((4-methyl-piperazin-1-yl)methyl)-3-phenylacrylamide 14b: Procedure similar to that of 14a.

The reaction of acid 28 (130 mg, 0.50 mmol), with amine 29 (168 mg, 0.60 mmol) yielded 180 mg (74%) of 14b as pale cream solid. Mp 122 – 125 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 11.05 (br s, 1H), 10.42 (s, 1H), 8.04 (s, 1H), 8.01 (d, $J = 8.7$ Hz, 1H), 7.96 (s, 1H), 7.68 (d, $J = 8.4$ Hz, 1H), 7.20 – 7.44 (m, 5H), 4.39 (d, $J = 4.5$ Hz, 2H), 3.53 (s, 2H), 2.37 – 2.93 (m, 8H), 2.31 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$): δ (ppm) 169.7, 167.9, 142.7, 141.3, 135.6, 134.7, 133.7 (q, $J = 32.6$ Hz), 129.1, 128.9, 128.5, 128.5, 122.1 (q, $J = 274.1$ Hz), 121.8, 117.2 (q, $J = 4.9$ Hz), 115.6, 103.7 (m), 54.8 (2C), 52.3, 45.8, 45.3; ESIMS: m/z calculated for C$_{25}$H$_{20}$F$_3$N$_5$O$_2$ (M+H)$^+$ 486.21, found 486.22; HPLC purity 98.4%.
Figure 23. 400 MHz $^1$H NMR of Compound 18a in CDCl$_3$
Figure 24. 101 MHz $^{13}$C NMR of Compound 18a in CDCl$_3$
Figure 25. 400 MHz $^1$H NMR of Compound 18b in CDCl$_3$
Figure 26. 101 MHz $^{13}$C NMR of Compound 18b in CDCl$_3$
Figure 27. 400 MHz $^1$H NMR of Compound 18c in CDCl$_3$
Figure 28. 101 MHz $^{13}$C NMR of Compound 18c in CDCl$_3$
Figure 29. 400 MHz $^1$H NMR of Compound 30a in CDCl$_3$
Figure 30. 101 MHz $^{13}$C NMR of Compound 30a in CDCl$_3$
Figure 31. 400 MHz $^1$H NMR of Compound 30b in CDCl$_3$
Figure 32. 101 MHz $^{13}$C NMR of Compound 30b in CDCl$_3$
Figure 33. 400 MHz $^1$H NMR of Compound 30c in CDCl$_3$
Figure 34. 101 MHz $^{13}$C NMR of Compound 30c in CDCl$_3$
Figure 35. 400 MHz $^1$H NMR of Compound 12a in CDCl$_3$
Figure 36. 101 MHz $^{13}$C NMR of Compound 12a in CDCl$_3$
Figure 37. 400 MHz $^1$H NMR of Compound 12b in CDCl$_3$
Figure 38. 101 MHz $^{13}$C NMR of Compound 12b in CDCl₃
Figure 39. 400 MHz $^1$H NMR of Compound 12c in CDCl$_3$
Figure 40. 101 MHz $^{13}$C NMR of Compound 12c in CDCl$_3$
Figure 41. 400 MHz $^1$H NMR of Compound 12d in CDCl$_3$
Figure 42. 101 MHz $^{13}$C NMR of Compound 12d in CDCl$_3$
Figure 43. 400 MHz $^1$H NMR of Compound 12e in CDCl$_3$
Figure 44. 101 MHz $^{13}$C NMR of Compound 12e in CDCl$_3$
Figure 45. 400 MHz $^1$H NMR of Compound 12f in CDCl$_3$
Figure 46. 101 MHz $^{13}$C NMR of Compound 12f in CDCl$_3$
Figure 47. 400 MHz $^1$H NMR of Compound 25b in DMSO-d$_6$
Figure 48. 101 MHz $^{13}$C NMR of Compound 25b in DMSO-$d_6$
Figure 49. 400 MHz $^1$H NMR of Compound 25c in DMSO-$d_6$. 
Figure 50. 101 MHz $^{13}$C NMR of Compound 25c in DMSO-d$_6$
Figure 51. 400 MHz $^1$H NMR of Compound 13a in CDCl$_3$
Figure 52. 101 MHz $^{13}$C NMR of Compound 13a in CDCl$_3$
Figure 53. 400 MHz $^1$H NMR of Compound 13b in CDCl$_3$
Figure 54. 101 MHz $^{13}$C NMR of Compound 13b in CDCl$_3$
Figure 55. 400 MHz $^1$H NMR of Compound 13c in CDCl$_3$
Figure 56. 101 MHz $^{13}$C NMR of Compound 13c in CDCl$_3$
Figure 57. 400 MHz $^1$H NMR of Compound 14a in CDCl$_3$
Figure 58. 101 MHz $^{13}$C NMR of Compound 14a in CDCl$_3$
Figure 59. 400 MHz $^1$H NMR of Compound 14b in CDCl$_3$
Figure 60. 101 MHz $^{13}$C NMR of Compound 14b in CDCl$_3$
References


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