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PII: S0968-0896(16)30706-4
DOI: http://dx.doi.org/10.1016/j.bmc.2016.09.019
Reference: BMC 13272

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 11 July 2016
Revised Date: 26 August 2016
Accepted Date: 8 September 2016

Please cite this article as: Ofori, E., Zhu, X.Y., Etukala, J.R., Bricker, B.A., Ablordeppey, S.Y., Synthesis and evaluation of the structural elements in alkylated tetrahydroisoquinolines for binding to CNS receptors, *Bioorganic & Medicinal Chemistry* (2016), doi: http://dx.doi.org/10.1016/j.bmc.2016.09.019

# Synthesis and evaluation of the structural elements in alkylated tetrahydroisoquinolines for binding to CNS receptors

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**Abstract**

Diseases of the CNS are often complex and involve multiple receptor systems and thus, the treatment options for these diseases must focus on targeting the multiple receptors implicated in the various disorders. Schizophrenia and depression are examples of such diseases and their pharmacotherapy thus depends on agents which target multiple receptors including the dopamine, serotonin and even cholinergic receptors at the same time. In our previous campaign to find multi-receptor ligands, we have identified the benzothiazole **1a** as an initial lead molecule. In the current work, we have expanded the structure affinity relationship (SAFIR) of **1a** resulting in the identification of a partially restrained butyrophenone **3j** as a potent and selective dual 5-$HT_{1A}$ and 5-$HT_7$ receptor ligand. It is expected that compound **3j** may serve as a new lead for further development in our search for newer and novel ligands with the potential to treat diseases of CNS origin.



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**Key words:** Structure affinity relationship, CNS ligands, antipsychotic, multi-receptor ligands, dual receptor ligands

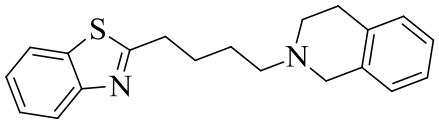
## 1. Introduction

Over the years, it has become evident that pharmacotherapy of major CNS diseases such as depression, bipolar disorder, schizophrenia and anxiety disorders rely on drugs which target multiple CNS receptors simultaneously.[1, 2] For instance, the superior efficacy and improved side effect profiles of atypical antipsychotics such as lurasidone, ziprasidone and aripiprazole, have been attributed to their broad spectrum of activities involving dopaminergic, serotonergic and even cholinergic neurotransmission.[3] In the same way, antidepressants such as vilazodone, that target the reuptake of serotonin (5-HT) along with the 5-$HT_{1A}$ receptor are known to be fast acting, efficacious and tolerable.[4, 5] However, a more defined combination of pharmacological activities at these and other targets is desirable for such agents to offer optimum therapeutic benefits in treating diseases of CNS origin.

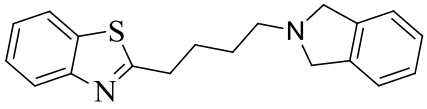
It is now well established that targeting the $D_2$-like receptors ($D_2$, $D_3$ and $D_4$, antagonists), 5-$HT_{1A}$ (agonists), 5-$HT_{2A}$ (antagonists) and 5-$HT_7$ (antagonists) are desirable features in the pharmacotherapy for schizophrenia.[6, 7] On the other hand, antidepressants may benefit from targeting the serotonin transporter (SERT), along with 5-$HT_{1A}$R (agonist) and 5-$HT_7$R (antagonist) for an improved profile.[8-10] And now with the introduction of the $D_2$R partial agonist and functionally selective aripiprazole as a well-tolerated and effective antipsychotic, the drug development paradigm for schizophrenia has significantly shifted in a new and exciting direction.[11] The caveat for multiple receptor targeting has been that it may also lead to off-target activities that may culminate in unforeseen side effects. Therefore, as part of our drug design strategy, there is also a focus on evaluating synthetic compounds at culprit receptors including the 5-$HT_{2B}$, receptors associated with valvular heart disease,[12] and the 5-$HT_{2C}$ and $H_1$ weight gain and sedation side effects.[13-14]

N-alkylated tetrahydroisoquinolines have been at the center of discussion recently as key ligands for certain CNS receptors associated with major brain disorders.[15-17] We have previously reported that the tetrahydroisoquinoline (THIQ) moiety, appropriately substituted with arylalkyl groups such as benzothiazole alkyl groups or halobutyrophenones could produce agents that provide differential binding profiles at clinically relevant CNS receptors including serotonin (5-HT) and dopamine (DA) receptor subtypes.[18, 19] In this manuscript, we further explore changes in three segments (A, B and C) of compound

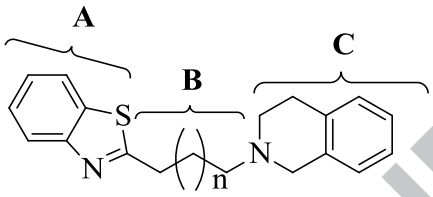
**1a (Figure 1**) in order to understand the structure-affinity relationships (SAFIRs) associated with this lead molecule.



Compound **1a**



Compound **1c**

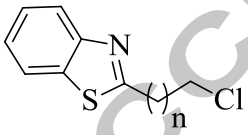



Areas targeted for modification (**A, B** and **C)**

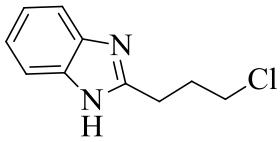
**Figure 1.** Structures of the benzothiazole hit compounds depicting the various segments of modification.

## 2. Chemistry

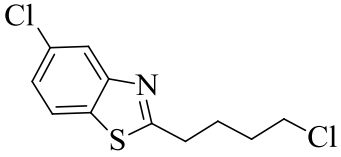
Compounds **1a** and **1c** were previously reported**.**[18] Compound **1b** was prepared by coupling 2-(3-chloropropyl)benzo[d]thiazole (**A**) previously reported by us[18,20-21] (**Figure 2**) to 1,2,3,4-tetrahydro-isoquinoline (THIQ) under the general alkylation condition **B** (4.1.2) that used $K_2CO_3$ as the base, KI as a catalyst and either acetonitrile ($CH_3CN$) or dimethoxyethane (DME) as the refluxing solvent. Alkylating agent **C** was synthesized according to a modified literature method[22] outlined in **Scheme 1** and was reacted with THIQ to afford compound **1d (Scheme 2**). Compound **1e** was prepared in a similar manner as **1b** except that 8-chloro-1,2,3,4-tetrahydroisoquinoline was used in place of THIQ, and **B** was the alkylating agent. The alkylating agent **D** was obtained using a similar approach as was used to obtain alkylating agents **A** and **B** and was reacted with the various amines (THIQ, aromatic substituted THIQs and decahydroisoquinoline) as depicted in **Scheme 2** to afford the corresponding compounds **1f-i**.




**A;** n = 2
**B;** n = 3




**C**




**D**

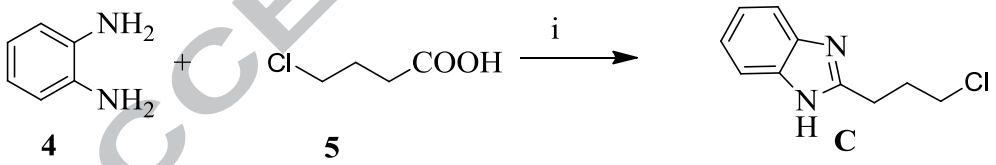
**Figure 2.** Alkylating agents used in the syntheses of compounds in group 1 (**1a – i)**.

To synthesize the indene **2a** and the 1,2-dihydronaphthalene analog, **2b** in group 2, the alkylating agents **14** and **15** were prepared following a four-step procedure (**Scheme 3**). First, the commercially available indanone **6** and the α-tetralone **7** were separately refluxed with glyoxylic acid in an aqueous acid in a cross-

aldol condensation reaction to produce the α,β-unsaturated ketones **8** and **9** respectively. The α,β-unsaturated keto function in **8** and **9** was then reduced using a palladium-carbon catalyzed hydrogenation reaction to afford the corresponding keto-acids **10** and **11** which were subsequently converted to the alcohols **12** and **13** under reductive conditions using $LiAlH_4$. The primary hydroxyl group was converted to an iodo group under Appel reaction conditions.[23] Interestingly, the Appel reaction also led to the generation of a styrene-like double bond seen in intermediates **14** and **15** (**Scheme 3**).

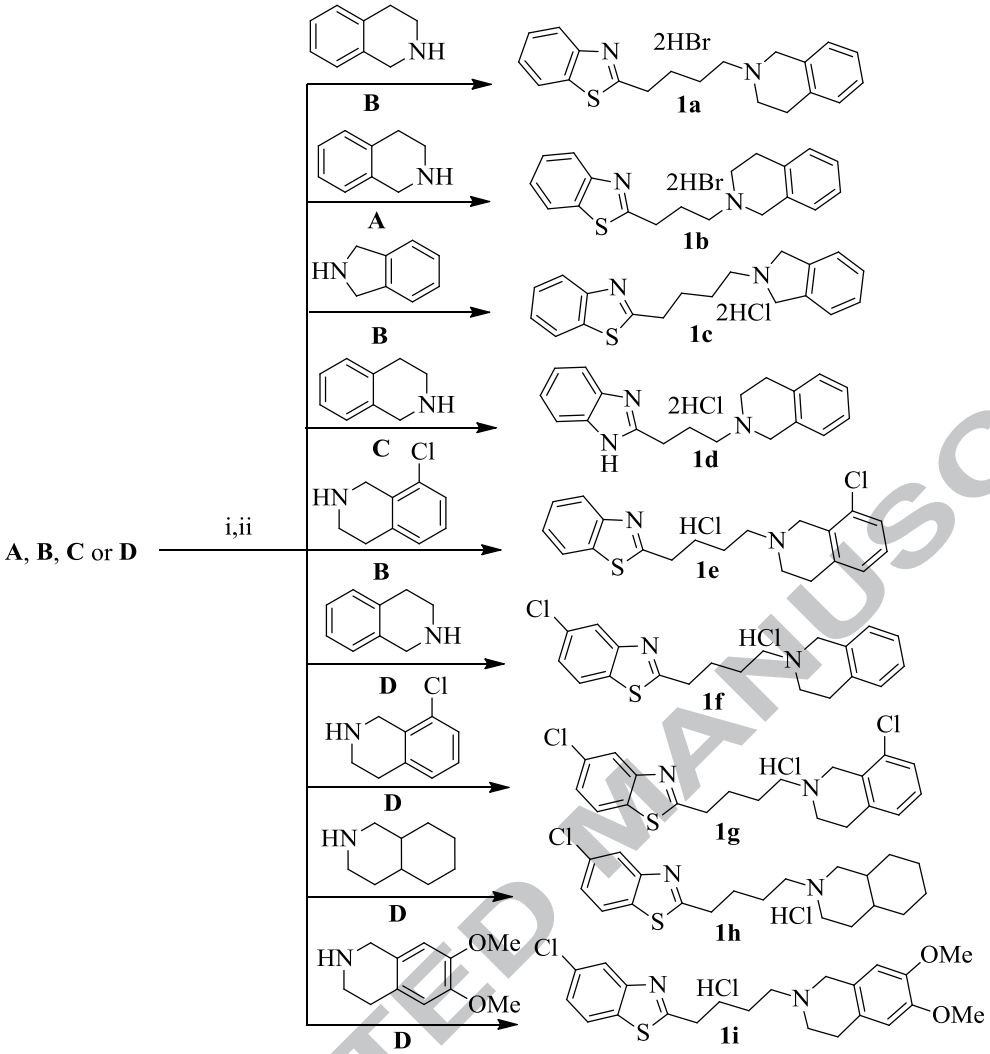
The bis-*p*-chlorobenzene alkylating agent **19** used to prepare compound **2c** was serendipitously isolated in a previous attempt to form intermediate **17** from a reaction of the commercially available Grignard reagent **16** and 4-chlorobutyryl chloride (**Scheme 4**). A plausible mechanism to explain the formation of this product is that the intended product **17** underwent further 1,2 addition of the Grignard reagent (4-chlorophenyl)magnesium chloride (**16**) to the carbonyl function to generate the tertiary alcohol **18** that dehydrated in the presence of $MgCl_2$ acting as a Lewis acid (catalyst) to produce **19**. The isolated alkylating agent **19** was then coupled to THIQ under the general alkylation condition **B** to afford **2c** (**Scheme 4**). In **Scheme 5**, the dimethylglutarimide analogs **2d** and **2e** were obtained through a simple two-step reaction. Commercially available dimethylglutarimide **20** was N-alkylated using dibromobutane and the resulting alkylbromide **21** coupled separately to THIQ and isoindoline to afford compounds **2d** and **2e** respectively (**Scheme 5**).

Compounds **3c-f** were obtained via a one-step N-alkylation with the commercially available 4-chloro-1-(4-chlorophenyl)butane-1-one,.**22** of the various amines (tetrahydroquinoline and tetrahydrobenzazepines) as depicted in **Scheme 6.** To prepare compound **3g**, oxindole **23** was acylated under Friedel-Crafts acylation conditions to obtain the ketone **24** which was subsequently used to react with THIQ to obtain compound **3g** (**Scheme 7**). Preparation of compounds **3c-g** and **3i** utilized microwave heating (general alkylation method **A**) that led to reduced reaction time (up to 60 min) and higher yields compared to conventional heating (general alkylation method **B**) (24-48 h). Compounds **3h-j** were prepared by N-alkylating THIQ using the indanone alkylating agents **25-27** previously reported by our lab (**Scheme 8**).[20, 21]

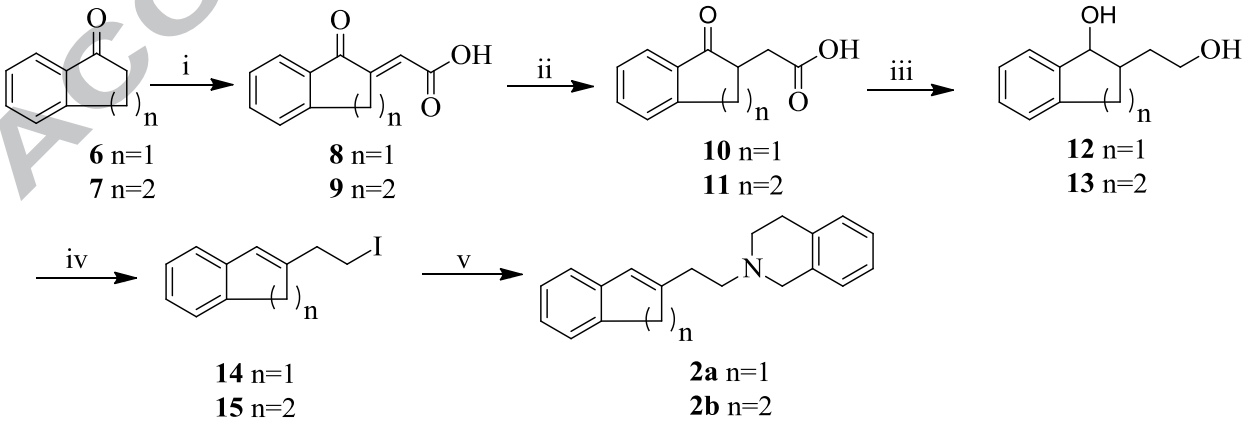



**4** **5** **C**

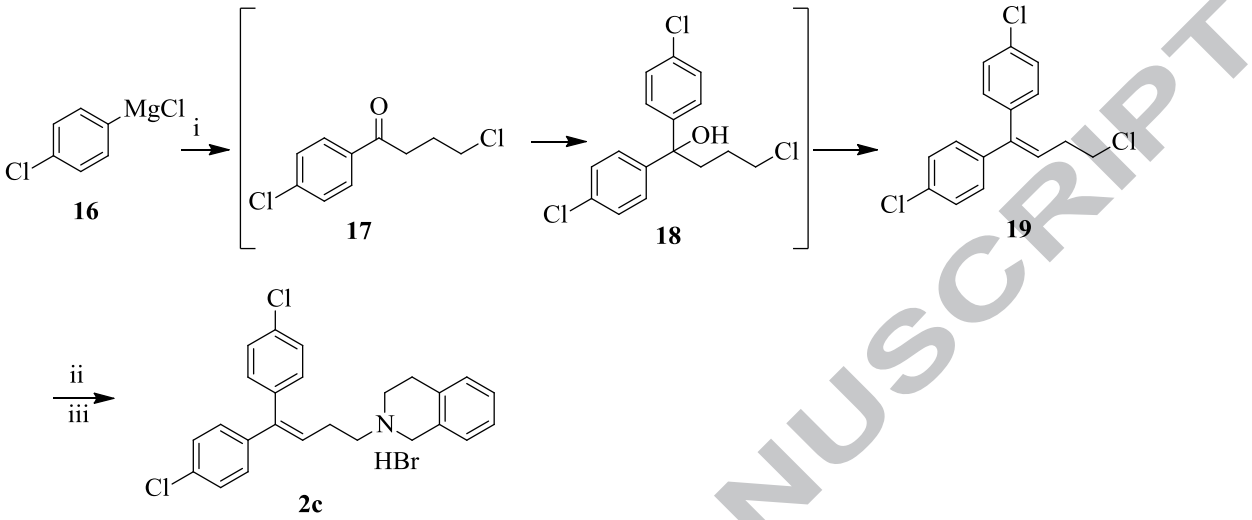
**Scheme 1.** Synthesis of alkylating agent **C.** Reagents and conditions: 5N HCl, reflux.



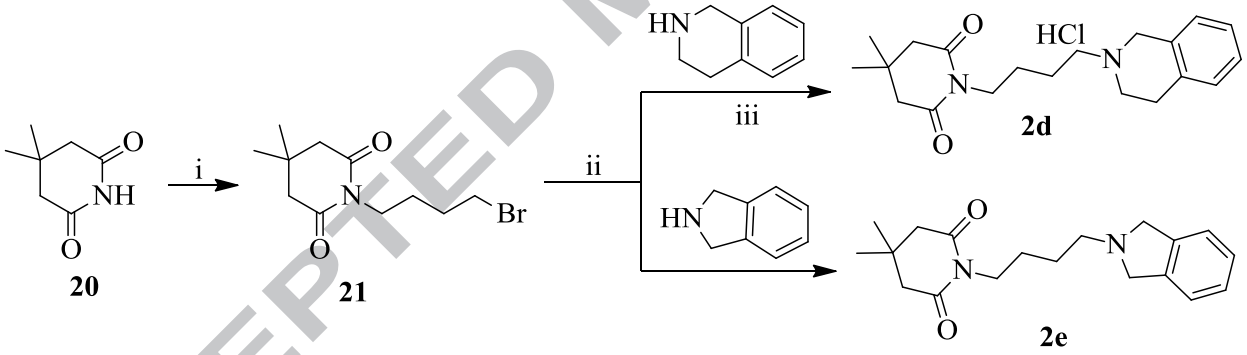

**Scheme 2**. Synthesis of compounds in Group 1. Reagents and conditions: i) $K_2CO_3$ ($Et_3N$ for **1d**), KI, DME, $CH_3CN$, or DMF (for **1d**), reflux or rt (for **1d**), 12-18h.; ii) ethereal HCl or HBr.



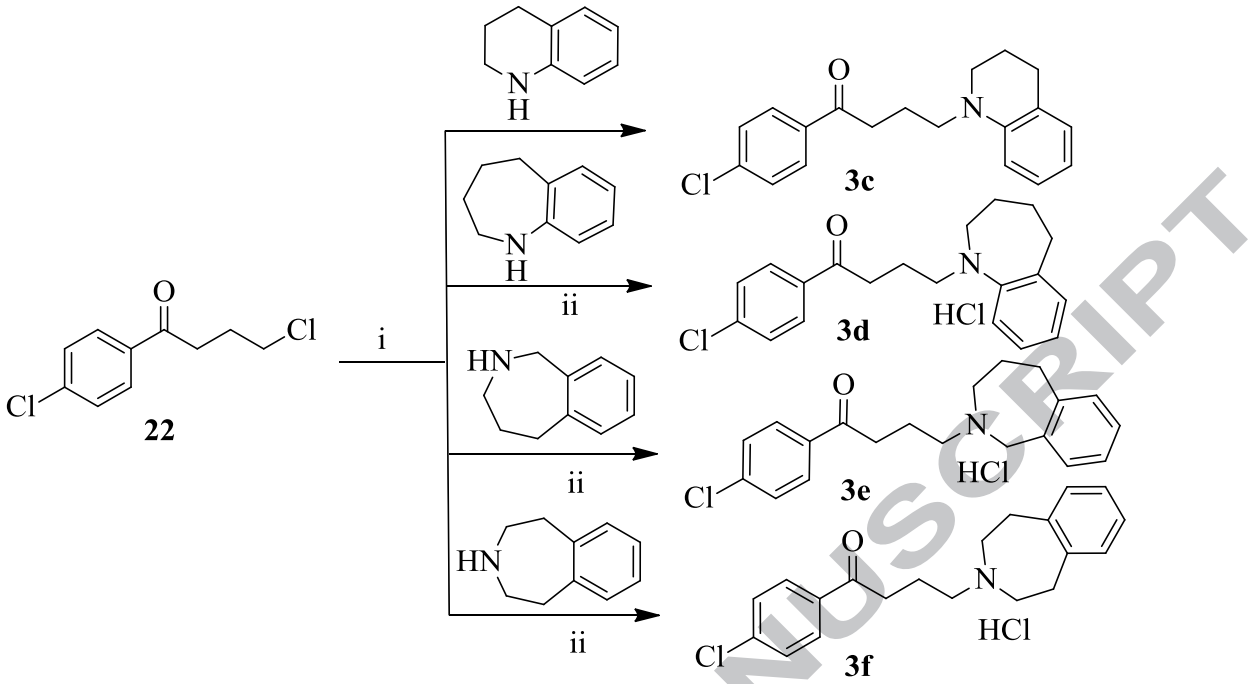
**Scheme 3.** Synthesis of the indene and dialin derivatives of THIQ. Reagents and conditions: i) glyoxylic acid, $H_2SO_4$-$H_2O$ (1:4), dioxane, reflux; ii) Pd/C ($H_2$), 40 psi, 48h; iii) $LiAlH_4$, toluene/ether, reflux ; iv) $PPh_3$, $I_2$, imidazole, DCM; v) $K_2CO_3$, KI, $CH_3CN$, reflux.



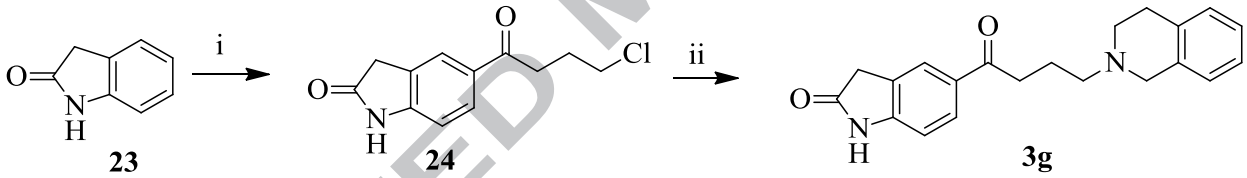

**Scheme 4.** Synthesis of bis-*p*-chlorophenyl analog of THIQ. Reagents and conditions: i) 4-chlorobutyryl chloride, dry THF, rt; ii) THIQ, $K_2CO_3$, KI, DME; iii) ethereal HBr.



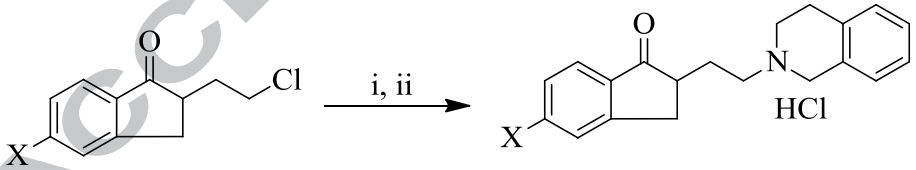

**Scheme 5.** Synthesis of dimethylglutarimide analogs of THIQ. Reagents and conditions: i) 1,4-dibromobutane, $CH_3CN$, reflux; ii) amine (THIQ for **2d**, and isoindoline for **2e**), $K_2CO_3$, $CH_3CN$, reflux; iii) ethereal HCl.




**Scheme 6.** Synthesis of *p*-chlorobutyrophenone analogs. Reagents and conditions: i) appropriate amine, $K_2CO_3$, KI, DME, MW; ii) ethereal HCl.




**Scheme 7.** Synthesis of the oxindole analog of THIQ. Reagents and conditions: i) 4-chlorobutyryl chloride, $AlCl_3$, $CS_2$, 0°-rt; ii) THIQ, $K_2CO_3$, KI, DME, MW.




**25** X= F
**26** X= H
**27** X= Cl

**3h** X=F
**3i** X=H
**3j** X=Cl

**Scheme 8**. Synthesis of indanone analogs of THIQ. Reagents and conditions: i) THIQ, $K_2CO_3$, KI, toluene, MW (for **3i**) or reflux (for **3h** and **3j**); ii) ethereal HCl for **3i** and **3j**.

## 3. Results and discussion

2-(4-(3,4-Dihydroisoquinolin-2(1H)-yl)butyl)benzo[d]thiazole (compound **1a)** was previously reported[18] and serves as a lead compound for modification to better understand the structure affinity relationship (SAFIR) associated with binding to key CNS receptors. The binding affinity data of compound **1a** at the $D_2$-like receptors (*Ki* : $D_2$ = 167 nM, $D_3$ = 8.7 nM and $D_4$ = 67 nM), 5-$HT_{1A}$ (*Ki* = 10 nM) and the 5-$HT_7$ receptor (*Ki* = 22 nM) are reported in **Table 1**. To this end, we embarked on an SAFIR study to explore the effect of structural changes in the benzothiazole moiety (segment A), the alkyl linker (segment B), and the tetrahydroisoquinoline moiety (segment C) of **1a** on binding affinity at the various CNS receptors. This study led to the generation of three structural types of compounds, the benzothiazoles, cycloalkyl/cycloalkylamines and butyrophenone analogs classified as group 1, 2, and 3 agents respectively, which will be the focus of this discussion.

Shortening the butyl linker in segment B of **1a** to a three-carbon chain (**1b),** led to a lower affinity for all the DA and 5-HT receptors investigated except at the $D_4$ receptor where a moderate increase in affinity was observed. Replacing the THIQ ring in **1a** with isoindoline (**1c)** also resulted in decreased binding affinity to all the receptors under consideration. Compound **1d** was prepared to explore the effect of replacing benzothiazole moiety (segment A) of compound **1b** with benzimidazole on binding affinity. The binding data suggest that the benzothiazole was preferred at all the receptors evaluated. Thus, the data on compounds **1a -d** suggests a benzothiazole with a 4-carbon spacer attached to THIQ is preferred for the DA and 5-HT receptors explored.

Compound **1e**, with an 8-chloro substitution on segment C of **1a** did not result in significant changes in binding affinities suggesting substitution on the THIQ ring is tolerated at least at the 8-position. Similarly, a 5-chloro substitution on the benzothiazole moiety (**1f**) was tolerated at all the receptors except for the $D_3$ and $D_4$ receptors. However, substituting the same substituents simultaneously on the benzothiazole and the THIQ moieties (1**g**) resulted in diminished affinities for all the receptors. Compound **1h** was synthesized to explore the need for the aromatic ring in THIQ for binding to the receptors under consideration. While the $D_2$ and $D_3$ receptors suffered significant reductions in affinity, the 5-$HT_{1A}$, 5-$HT_{2A}$, 5-$HT_{2C}$ and 5-$HT_7$ were essentially unaffected. Similarly, introducing the 9,10-dimethoxy group on **1f** to form **1i,** ill-affected binding affinity to the $D_2$-like receptors but not the serotonin receptors under consideration. It is worth noting that none of the benzothiazole analogs displayed high affinity *Ki* values for the "culprit" receptors $H_1$ and 5-$HT_{2C}$ which have been associated with metabolic and sedative side effects.[12-14] On the other hand, there is high affinity binding and significant variability in the binding to the 5-$HT_{2B}$ receptors with a range of 7.0 – 327 nM.

To further evaluate the structural requirements for segment A/B binding affinity, we synthesized four analogs, **2a – d** and the binding affinity constants are reported in **Table 2**. Compounds **2a** and **2b** can be viewed as partially restricted butyl spacers using cyclopentene and cyclohexene rings. Both compounds displayed diminished binding affinity for the $D_2$R and showed no definitive trends at other clinically relevant receptors. Compound **2c**, **2d** and **2e** generally showed no significant binding affinities for any of the receptors under consideration.

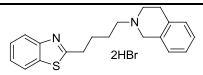
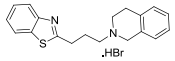
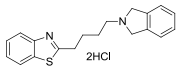
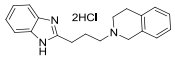
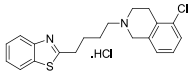
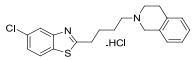
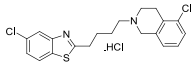
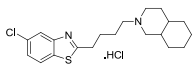
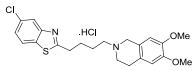
Compounds with the butyrophenone alkyl group (group 3) are analogs of either compound **3a** or **3b** previously reported by us.[19] Inspired by the promising binding affinity profiles of these butyrophenones at the relevant CNS receptors (**Table 3**), we embarked on an exploration to further understand the SAFIR of these compounds. To begin with, we sought to understand the role of the position of the nitrogen in segment C. The THIQ moiety in **3b** was replaced with tetrahydroquinoline and 2,3,4,5-tetrahydro-1H-benzo[*b*]azepine to produce compounds **3c** and **3d** respectively, resulting in the formation of aromatic nitrogen atoms in both analogs. Significantly, this change resulted in no apparent receptor binding affinity at the selected CNS receptors. This observation will lead one to speculate that an aliphatic nitrogen atom with a higher pKa is more desirable in these compounds for binding to the receptors. Alternatively, the positioning of the nitrogen atom proximal to the phenyl ring may have prevented optimal interaction with the complementary functional group at the receptors. Compounds **3e** and **3f** were synthesized to further explore the above trains of thought. Thus, moving the nitrogen away from a direct interaction with the phenyl ring resulted in a minor improvement in the binding potencies at the DA and 5-HT receptor subtypes when compared to **3c** and **3d** but fell way short of the original affinities seen with **3b**. Replacing the 4-chlorophenyl group with an oxindole bicyclic moiety to form **3g** produced no significant improvements in binding affinity at the various receptors.

Compounds **3h**-**3j** were the partially restrained analogs of the butyrophenone analogs **3a** or **3b**. Restricting the keto group into an indanone led to some rather interesting observations as reported in **Table 3**. First, compound **3h**, the restrained analog of **3a**, records over 15-fold decrease in potency at the $D_2R$ (*Ki* = 750 nM), compared to **3a** (*Ki* = 49 nM), retained activity at the 5-$HT_{1A}$ (*Ki* = 19 nM) and an awe-inspiring low nanomolar binding affinity at the 5-$HT_7$ receptor (*Ki* = 1.6 nM). This is of biological significance because of the paucity of selective dual 5-$HT_{1A}$ and 5-$HT_7$ receptor ligands in the literature.[24] Also, a growing body of knowledge suggests that the 5-$HT_7$ receptor controls normal circadian rhythm, sleep, mood, memory and learning, and cognition[25-27] and may therefore serve as a plausible target for treating neuropsychiatric disorders such as schizophrenia and mood disorders. Having obtained **3h** as a possible lead, we investigated the effect of removing the fluoro group in **3h** to produce compound **3i**. This resulted in over 165-fold decrease in binding affinity at the 5-$HT_7$ receptor which suggested that a halo-phenyl moiety may be required for this 5-$HT_7$ affinity. Further confirmation of this thought was observed by replacing the fluoro atom with a chloro atom to form compound **3j** with a sub-nanomolar binding affinity constant (*Ki* = 0.5 nM) at the 5-$HT_7$ receptor. Compound **3j** compares favorably with the binding affinity of SB269970 (*pKi* = 1.3 nM), the selective 5-$HT_7$ antagonist, albeit it has a dual binding affinity profile.[28] Similarly, when compared to the most potent analogs from modifications to the lead compound, UCM-5600[29] and a recently reported arylindole series,1-(naphthyl)indole derivative **3p**,[30] compound **3j** is about 9 to14-fold more potent at the 5-$HT_7$ receptor and over 4 to 10-fold higher affinity at the 5-$HT_{1A}$ receptor. Overall, the binding affinity constants of the indanone analogs fared poorly at the $D_2$-like receptors as well as the culprit 5-HT receptors.

In conclusion, beginning with compound **1a** as an initial lead molecule of the benzothiazole series, we have obtained several alkylated THIQ analogs with potent and desirable multi-receptor binding features

especially at the 5-$HT_{1A}$ and 5-$HT_7$ receptors. The 5-chloro-indanone analog **3j**, displaying low nanomolar and a sub-nanomolar affinity values at the 5-$HT_{1A}$ and the 5-$HT_7$ receptors respectively, is an addition to the rather scarce group of dual 5-$HT_{1A}$ and 5-$HT_7$ receptor selective ligands in the literature that can be used to probe the role of these receptors in treating the affective and cognitive diseases of CNS origin.

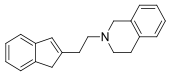
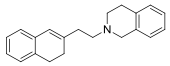
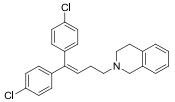
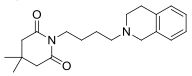
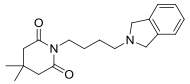
**Table 1**
Group 1 analogs and their binding affinity constants at clinically relevant CNS receptors

| Compd | Structure | *Ki* (nM) (pKi±SEM) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | $D_2$ | $D_3$ | $D_4$ | 5-$HT_{1A}$ | 5-$HT_{2A}$ | 5-$HT_7$ | 5-$HT_{2B}$ | 5-$HT_{2C}$ | $H_1$ |
| **1a*** |  | 167 (6.78±0.09) | 8.7 (8.5±0.1) | 67.0 (7.17±0.05) | 10.0 (8±0.03) | 1681 (5.77±0.06) | 22.0 (7.66±0.06) | 18.0 (7.74±0.05) | 910 (6.04±0.04) | 583 (6.23±0.08) |
| **1b** |  | MTA | 80.0 (7.1±0.10) | 41.0 (7.39±0.04) | 95.0 (7.02±0.03) | 2051 (5.69±0.06) | 37.0 (7.43±0.07) | 18.0 (7.74±0.04) | 1182 (5.93±0.05) | 822 (6.09±0.08) |
| **1c*** |  | 990 (6±0.04) | 259 (6.59±0.06) | 141 6.85±0.07 | 111 (6.95±0.07) | >10,000 | 211 (6.68±0.08) | 135 (6.87±0.06) | MTA | 762 (6.12±0.08) |
| **1d** |  | 915.0 6.09±0.09 | 2176 5.66±0.07 | 127.0 6.9±0.07 | 65.0 7.19±0.07 | >10K | 91.0 7.04±0.04 | MTA | >10K | 290 ± 40 |
| **1e** |  | 272 (6.57±0.08) | 31.0 (7.52±0.04) | 129 (6.89±0.08) | 29.0 (7.53±0.08) | 258 (6.6±0.10) | 45.0 (7.35±0.04) | 239 (6.62±0.08) | 675 (6.17±0.09) | 293 (6.53±0.08) |
| **1f** |  | 138 (6.86±0.08) | 447 (6.35±0.07) | 572 (6.24±0.09) | 15.0 (7.84±0.07) | 702 (6.2±0.10) | 25.0 (7.6±0.09) | 16.0 (7.81±0.07) | 759 (6.12±0.08) | 247 (6.61±0.06) |
| **1g** |  | 853 (6.07±0.08) | 91.0 (7.04±0.05) | 279 (6.55±0.08) | 42.0 (7.38±0.08) | 483 (6.3±0.1) | 144 (6.84±0.04) | 327 (6.49±0.09) | 820 (6.09±0.09) | 560 (6.25±0.07) |
| **1h** |  | 1087 (5.96±0.08) | 526 (6.28±0.08) | 37.0 (7.43±0.06) | 11.0 (7.93±0.06) | 1144 (5.9±0.10) | 44.0 (7.36±0.07) | 64.0 (7.19±0.09) | 501 (6.3±0.07 | 268 (6.57±0.06) |
| **1i** |  | 418 (6.38±0.09) | 1083 (5.97±0.07) | 272 (6.57±0.07) | 9.9 (8±0.05) | 667 (6.2±0.1) | 67.0 (7.17±0.06) | 7.0 (8.15±0.08) | 329 (6.48±0.08) | 327 (6.49±0.08) |

MTA = Missed 50% of threshold inhibition.
* Binding affinity data from [18]

**Table 2**

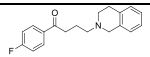
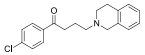
Compounds in group 2 and their binding affinity constants at relevant CNS receptors

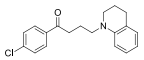
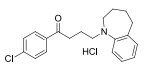
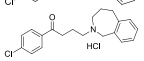
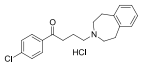
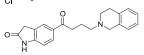
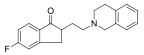
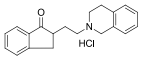
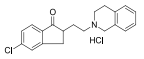
| Compd | Structure | *Ki* (nM)* (*pKi* ± SEM) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | $D_2$ | $D_3$ | $D_4$ | 5-$HT_{1A}$ | 5-$HT_{2A}$ | 5-$HT_7$ | 5-$HT_{2B}$ | 5-$HT_{2C}$ | H1 |
| **2a** |  | MTA | 88.0 (7.05±0.09) | 194 (6.71± 0.04) | 1,109 (5.96 ±0.08) | 1,867 (5.73±0.04) | 132 (6.88±0.07) | 149 (6.83±0.07) | MTA | MTA |
| **2b** |  | 5,647 (5.25±0.06) | 184 (6.73±0.04) | 140 (6.85±0.05) | 138 (6.86 ±0.04) | 975 (6.01 ± 0.09) | 65.0 (7.18 ± 0.07) | 126 (6.9±0.04) | 2,903 (5.54 ± 0.07) | 1437 (5.84 ± 0.07) |
| **2c** |  | MTA | 150 (6.8 ± 0.1) | MTA | MTA | MTA | 497 (6.3±0.07) | MTA | 2,028 (5.69±0.05) | 998 (6 ± 0.07) |
| **2d** |  | MTA | 1,645 (5.8 ± 0.1) | MTA | MTA | MTA | MTA | MTA | MTA | MTA |
| **2e** |  | 2,933 (5.53±0.09) | >10,000 | >10,000 | 339 (6.47±0.07) | >10,000 | 739 (8.2 ± 0.1) | 531 (6.28±0.07) | 305 (6.53±0.07) | 3,867 (5.41±0.07) |

MTA = Missed 50% of threshold inhibition.

**Table 3**

Compounds in group 3 and their binding affinity at clinically relevant CNS receptors

| Compd | Structure | *Ki*(nM) (p*Ki* ± SEM) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | $D_2$ | $D_3$ | $D_4$ | 5-$HT_{1A}$ | 5-$HT_{2A}$ | 5-$HT_7$ | 5-$HT_{2B}$ | 5-$HT_{2C}$ | H1 |
| **3a**** |  | 49.0 ±3.0 | 72.0 ±5.0 | 2.3 ±0.2 | 19.5 | 21.0 | 381 | 519 | >10,000 | 86.3± 7.3 |
| **3b**** |  | 126 (6.9±0.06) | 17.0 (7.77±0.04) | 86.0 (7.07±0.04) | 8.2 (8.09±0.07) | MTA | 3.6 (8.45±0.07) | 232 (6.63±0.07) | 2,976 (5.53±0.06) | 597 (6.22±0.05) |
| **3c** | | | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| |  | MTA | MTA | MTA | MTA | MTA | MTA | MTA | >10,000 | MTA |
| **3d** |  | MTA | MTA | MTA | MTA | MTA | MTA | MTA | MTA | MTA |
| **3e** |  | 3,578 (5.45±0.08) | 342 (6.47±0.04) | 442 (6.35±0.04) | 1,712 (5.77±0.07) | 120 (6.92±0.03) | 257 (6.59±0.05) | 501 (6.3±0.05) | 348 (6.46±0.04) | 3,224 (5.5±0.1) |
| **3f** |  | 1,170 (5.93±0.08 | 106 (6.97±0.04) | 82 (7.09±0.04) | 214 (6.67±0.06) | 281 (6.55±0.03) | 138 (6.68±0.05) | 549 (6.26±0.05) | 611 (6.21±0.07) | 1,087 (6±0.3) |
| **3g** |  | 5,399 (5.27±0.09) | 66 (7.18±0.04) | 3,335 (5.48±0.04) | 122 (6.91±0.07) | 1,022 (5.99±0.03) | 127 (6.9±0.05) | 483 (6.32±0.05) | 4,234 (5.37±0.09) | MTA |
| **3h** |  | 750 (6.12±0.07) | 223 (6.65±0.04) | 251 (6.6±0.06) | 19.0 (7.73±0.04) | 1,204 (5.92±0.09) | 1.6 (8.8±0.06) | 294 | MTA | ND |
| **3i** |  | 2,583.5 | 866.0 | 1,102 | 48.3 | 391.3 | 265 | 391 | 1,184 (5.93±0.06) | 24 (7.6±0.1) |
| **3j** |  | 946 (6.02±0.08) | 783 (6.11±0.07) | 50 (7.3±0.06) | 16 (7.81±0.06) | 748 (6.1±0.1) | 0.5 (9.33±0.06) | 109 (6.96±0.07) | 128 (6.89±0.08) | 553 (6.26±0.06) |
| | [a]SB269970 | ND | ND | ND | <5 | <5 | 1.3<br>8.9±0.1 | 5 | <5 | ND |
| | [b]Compound **18** | ND | ND | ND | 219±11 | ND | 7±2 | ND | ND | ND |
| | [c]Compound **3p** | ND | ND | ND | 70±12 | ND | 4.5±1 | ND | ND | ND |

MTA = Missed 50% of threshold inhibition, ND = Not determined.

* Ki values without the associated SEM, are within 20% of the mean value. ** Binding affinity data from reference 19.

[a]Binding affinity data from reference 28. [b]Binding affinity data from reference 29; [c]Binding affinity data from reference 30

## 4. Experimental

Melting points of final compounds were determined on a Gallenkamp (UK) apparatus and are reported as uncorrected. All NMR spectra were obtained on a Varian 300 MHz Mercury Spectrometer and the free induction decay (FID) data were processed using Mestrelab's Mnova NMR software (version 8.1) to obtain the reported NMR data. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA, and are within 0.4% of theory unless otherwise stated. Flash chromatography was performed using CombiFlash® with Davisil grade 634 silica gel. Starting materials were obtained from Sigma–Aldrich or Matrix scientific and were used without further purification. All microwave assisted syntheses (MW) were carried out using a Biotage Initiator®.

### 4.1.1 General alkylation procedure A

A mixture of alkylating agent (1 equiv), appropriate amine (1.1 equiv) $K_2CO_3$ (1.1 equiv), and KI (catalytic) in DME or $CH_3CN$ (10 mL) was placed in a 20 mL microwave vial (for MW) with a stirrer and tightly sealed. The mixture was subjected to microwave (MW) heating at 120 $^oC$ for 60 mins. The resulting crude mixture was directly purified on silica gel by flash chromatography (gradient up to 70% EtOAc in hexanes) to afford the final compounds. The free base where necessary, was converted to the HCl or HBr salt and crystallized out of a mixture of MeOH-$Et_2O$.

### 4.1.2 General alkylation procedure B

A mixture of alkylating agent (1 equiv), appropriate amine (1.1 equiv) $K_2CO_3$ (1.1 equiv), and KI (catalytic) in DME or $CH_3CN$ (50 mL) was placed in a round bottomed flask with a stirrer was heated to reflux on a heating plate for 24-28 h. The reaction was monitored by TLC for product formation. After reaction was complete, the resulting crude mixture was directly purified on silica gel by flash chromatography (gradient up to 70% EtOAc in hexanes) to afford the final compounds. The free base where necessary, was converted to the HCl or HBr salt and crystallized out of a mixture of MeOH-$Et_2O$.

### 4.2. Synthesis of Compounds

#### 4.2.1. 2-(3-(3,4-Dihydroisoquinolin-2(1H)-yl)propyl)benzo[d]thiazole hydrobromide, 1b

Previously reported alkylating agent 2-(3-chloropropyl)benzo[d]thiazole[18] was reacted with THIQ under the general alkylation conditions **B** (4.1.2) described above to produce the hygroscopic compound **1b** as the HBr salt in 20% yield. $^1$H NMR (DMSO-$d_6$): 9.96 (brs, 1H), 8.08 (d, $J$ = 7.5 Hz, 1H), 7.93 (d, $J$ = 7.5 Hz, 1H), 7.50 (t, $J$ = 7.5 Hz, 1H), 7.42 (t, $J$ = 7.5 Hz, 1H), 7.20-7.30 (m, 4H), 4.61 (d, $J$ = 13.8 Hz, 1H), 4.34 (dd, $J$ = 7.8, 15.6 Hz, 1H), 3.74-3.79 (m, 1H), 3.34-3.42 (m, 3H), 3.23-3..28 (m, 2H), 3.02-3.18 (m, 2H), 2.30-2.40 (m, 2H). Anal. calcd for $C_{19}H_{22}Br_2N_2S$: C 48.53, H 4.72, N 5.96. Found: C 48.61, H 4.72, N 5.89.

#### 4.2.2. 2-(3-Chloro-propyl)-1H-benzoimidazole, D

To a mixture of 1,2-diaminobenzene,**4** (0.5g, 4.6 mmol) and 4-chlorobutanoic acid,**5** (0.86 g, 7 mmol) in a schlenk tube was added 5N HCl solution (25 mL) and heated to boil for 5 h. The reaction mixture was

then cooled and added to water (25 mL). The precipitate obtained was filtered and vacuum dried to give a white solid (1.25 g, 56%) which was used in the next step without further purification.

**4.2.3. 2-(3-(1H-benzo[d]imidazol-2-yl)propyl)-1,2,3,4-tetrahydroisoquinoline, 1d**

A mixture of 2-(3-chloro-propyl)-1H-benzoimidazole, **D**, (1.2 g, 6.15 mmol), THIQ (1.2 g, 9.0 mmol), KI (100 mg) and $Et_3N$ (4 mL, 28.5 mmol) in DMF (5 mL) was stirred for 56 h at room temperature (rt). The mixture was diluted with EtOAc (200 mL), washed with brine (3 × 50 mL). The organic layer was dried over $Na_2SO_4$, and filtered. The filtrate was concentrated in vacuo to dry and followed by column chromatography on silica gel to afford 2-[3-(1H-benzoimidazol-2-yl)-propyl]-1,2,3,4-tetrahydro-isoquinoline, **1d** as the HCl salt (0.32 g ,14%) and crystallized from MeOH-$Et_2O$ mixture. Mp: 234-235 ºC; $^1$H NMR (DMSO-$d_6$): 7.77 (m, 2H), 7.50 (m, 2H), 7.22 (m, 4H), 4.45 (brs, 2H), 3.52 (brs, 2H), 3.34 (m, 4H), 3.15 (brs, 2H), 2.52 (m, 2H). Anal calcd for $C_{19}H_{23}Cl_2N_3$•$0.3H_2O$: C 61.72, H 6.27, N 11.37. Found: C 61.40, H 6.48, N 11.35.

**4.2.4. 2-(4-(8-Chloro-3,4-dihydroisoquinolin-2(1H)-yl)butyl)benzo[d]thiazole hydrochloride, 1e**

Using the previously reported alkylating agent 2-(4-chlorobutyl)-benzo[d]thiazole,[18] the amine 8-chloro-1,2,3,4-tetrahydroisoquinoline was N-alkylated under the general alkylation reaction condition B, described above to produce compound **1e** as a white HCl salt in 45% yield. Mp: 192-194 °C. $^1$HNMR (300 MHz, DMSO-$d_6$): δ 11.01 (brs, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 8.07 (d, *J* = 7.8 Hz,1H), 7.62-7.54 (m, 3H), 7.45 (t, *J* = 6.9 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 5.05-4.95 (m, 1H), 4.69 (d, *J* = 1.5 Hz, 1H), 4.47-4.40 (m, 1H), 3.89-3.85 (m, 1H), 3.48-3.32 (m, 4H), 3.22 (t, *J* = 5.1 Hz, 2H), 2.05 (s, 4H). Anal. calcd for; $C_{20}H_{22}Cl_2N_2S$•$0.9.H_2O$: C 58.65, H; 5.41, N; 6.84, Found; C; 58.43, H; 5.81, N; 6.36.

**4.2.5. Alkylating agent, 5-Chloro-2-(4-chlorobutyl)benzo[*d*]thiazole, C**

Using similar cyclization reaction procedure previously described by us,[18] 2-amino-4-chlorobenzenethiol was reacted with 5-chloropentanoyl chloride in toluene at rt to afford alkylating agent **C** (see ref[18] for details). $^1$H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, *J* = 2.1 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.34(dd, *J* = 1.8 Hz, 6.6 Hz, 1H), 3.59 (t, *J* = 6.6 Hz, 2H), 3.15 (t, *J* = 7.2 Hz, 2H), 2.08-2.01 (m, 2H), 1.96-1.89(m, 2H).

**4.2.6. 5-Chloro-2-(4-(3,4-dihydroisoquinolin-2(1H)-yl)butyl)benzo[*d*]thiazole hydrochloride, 1f**

Alkylating agent **C** was reacted with THIQ under the general alkylation condition B described above to afford compound **1f** as the HCl salt in 75% yield. Mp: 229-231 °C, $^1$H NMR (300 MHz, DMSO-$d_6$): δ 10.68 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 1.5 Hz,1H), 7.47-7.44 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.27-7.17 (m, 4H), 4.52-4.47 9d, *J* = 15.6 Hz, 1H), 4.28-4.21 (dd, *J* = 7.8, 15.3 Hz, 1H), 3.70-3.64 (m, 1H), 3.37 (s, 2H), 3.24-3.16 (m, 4H), 3.02-2.97 (m, 1H), 1.96-1.89 (m, 4H). Anal. calcd for $C_{20}H_{22}Cl_2N_2S$: C 61.07, H 5.64, N 7.12. Found: C 60.89, H 5.65, N 6.94.

**4.2.7. 5-Chloro-2-(4-(5-chloro-3,4-dihydroisoquinolin-2(1H)-yl)butyl)benzo[d]thiazole hydrochloride, 1g**

Using method **B** of the general alkylation reaction condition, 8-chloro-1,2,3,4-tetrahydroisoquinoline was N-alkylated with alkylating agent **C** to afford compound **1g** as a white solid HCl salt in 73% yield. Mp: 218-220°C, $^1$H NMR (300 MHz, DMSO-$d_6$): δ 11.70 (brs, 1H), 8.08 (d, *J* = 8.7 Hz, 1H,), 7.99 (d, *J* = 2.1 Hz, 1H), 7.47-7.42, (m, 2H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.8Hz, 1H), 4.55-4.5 (m, 1H), 4.32-4.24 (m, 1H), 4.02-3.97 (m, 2H), 3.36-3.18 (m, 4H), 3.06 (t, *J* = 5.1Hz, 2H), 1.89 (s, 4H). Anal. calcd for $C_{20}H_{21}Cl_3N_2S$•0.24.$H_2O$: C 55.58, H 4.90, N 6.48. Found: C 55.57, H 5.10, N 6.19.

**4.2.8. 5-Chloro-2-(4-(octahydroisoquinolin-2(1H)-yl)butyl)benzo[d]thiazole hydrochloride, 1h**

General alkylation method **B** was used. Alkylating agent C was reacted with decahydroisoquinoline to afford compound **1h** in 85% yield. Mp: 141-143°C. $^1$H NMR (300 MHz, DMSO-$d_6$): δ (9.93 (s, 1H), 8.11-8.08 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 1.8 Hz, 1H), 7.47-7.44 (dd, *J* = 2.1, 11.4 Hz, 1H) 3.50-3.30 (m, 4H), 3.25 (d, *J* = 10.2 Hz 1H), 3.18-3.13 (t, *J* = 7.2 Hz, 2H), 3.06-3.300 (m, 2H), 2.90-2.80 (m, 1H), 1.86-1.78 (m, 4H), 1.70-1.66 (m, 2H), 1.60-1.43 (m, 4H), 1.24-1.18 (t, *J* = 10.2 Hz, 2H), 1.00-0.87 (t, *J* = 12.0 Hz, 2H). Anal. calcd for $C_{20}H_{28}Cl_2N_2S$•0.95.$H_2O$: C 57.67, H 6.78, N 6.73. Found: C 57.66, H 7.08, N 6.51.

**4.2.9. 5-Chloro-2-(4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)butyl)benzo[d]thiazole hydrochloride, 1i**.

Compound **1i** in its HCl salt form was prepared similarly to **1h** above using 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline as the amine in a 79% yield. Mp: 180-182$^o$C, $^1$H NMR (300 MHz, DMSO-$d_6$): δ 10.60 (s, 1H), 8.09 (d, J = 9.0 Hz, 1H), 8.00 (d, *J* = 1.8 Hz, 1H), 7.47-7.44 (dd, *J* = 2.1, 8.4 Hz, 1H), 6.78 (d, *J* = 8.4Hz, 2H), 3.80-3.74 (m, 5H), 3.30-3.16 (m, 5H), 1.90-1.86 (m, 4H). Anal. calcd for $C_{20}H_{28}Cl_2N_2S$•0.32EtOAc: C 54.91, H 5.45, N 5.82. Found: C 54.76, H 5.84, N 5.54.

**4.2.10. (E)-2-(1-oxo-1*H*-inden-2(3*H*)-ylidene)acetic acid, 8**

A mixture of 1-indanone, **6** (3 g, 22.7 mmol), glyoxylic acid (50% aqueous solution, 5.9 g, 54.5 mmol), and conc. $H_2SO_4$ (0.74 mL) in dioxane (5 mL) were stirred at refluxing temperature for 12 h. The mixture was cooled, the product filtered off, washed with water and dried to give the acid *(E)*-2-(1-oxo-1*H*-inden-2(3*H*)-ylidene) acetic acid (3.68 g, 86.2%) as a white solid. Mp: 202–204 °C (lit. mp 205–206 °C), $^1$H NMR (300 MHz, DMSO-$d_6$): δ 12.00 (brs, 1H), 7.73–7.80 (m, 2H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 6.55 (t, *J* = 2.4 Hz, 1H), 4.08 (d, *J* = 1.8, 2H).

**4.2.11. (E)-2-(1-oxo-3,4-dihydronaphthalen-2(1H)-ylidene)acetic acid, 9**

Intermediate **9** was prepared similarly to **8** above using α-tetralone instead of 1-indanone (**Scheme 3**). The crude product obtained after filtration was used for the next step without further purification. Yield (3.5 g, 84%). $^1$H NMR (300 MHz, DMSO-$d_6$): 12.96 (brs, 1H), 7.95-7.92 (m, 1H), 7.83-7.57(m, 1H), 7.43-7.38(m, 2H), 6.65-6.64(m, 1H), 3.31-3.27(m, 2H), 2.98(t, *J* = 6.6 Hz, 2H).

**4.2.12. 2-(1-oxo-2,3-dihydro-1H-inden-2-yl)acetic acid, 10**

*(E)*-2-(1-oxo-1*H*-inden-2(3*H*)-ylidene) acetic acid, **8** (10 g, 53 mmol) in MeOH (45 mL) and dioxane (150 mL) with Pd/C (10%, 1 g) was stirred under $H_2$ (40 psi) for 48 h. The mixture was filtered through

celite and the solvent evaporated to give 2-(1-oxo-2,3-dihydro-1H-inden-2-yl)acetic acid (7) as an off-white solid. Mp 85–88°C, $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.47 (br s, 1 H, enol OH ), 7.08–7.18 (m, 4 H, H-4, H-5, H-6, H-7), 2.99–3.06 (m, 2 H, H-1, H-3), 2.69–2.74 (m, 1 H, H-2), 2.53–2.60 (m, 2 H, H-1, H-3), 2.48 (d, $J$ = 7.4 Hz, 2 H, $CH_2CO_2$).

**4.2.13. 2-(1-hydroxy-3,4-dihydronaphthalen-2-yl)acetic acid, 11**

Intermediate **11** was prepared similarly to **10** above using (E)-2-(1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)acetic acid(**9**) as the precursor (Scheme 3). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 12.13 (brs, 1H), 7.85(d, $J$ = 8.1Hz, 1H), 7.56-7.5(m, 1H), 7.35-7.31(m, 2H), 3.13-3.02(m, 1H), 2.95(m, 2H), 2.74-2.66(m, 1H), 2.44-2.37(m, 1H), 2.17-2.09(m, 1H), 2.0-1.85(m, 1H).

**4.2.14. 2-(2-hydroxyethyl)-2,3-dihydro-1H-inden-1-ol, 12**

A solution of 2-(3-Hydroxy-1*H*-inden-2-yl)acetic acid (3.4 g, 19.8 mmol) in dry THF (100 mL) was added dropwise to a suspension of $LiAlH_4$ (1.5 g, 39.6 mmol) in dry THF (50 mL) at 0 °C and the resulting mixture was stirred at refluxing temperature for 12 h. EtOAc was added to quench excess $LiAlH_4$ and then aqueous HCl solution (10%, 50 mL) was added and the organic fraction separated. The aqueous solution was extracted with EtOAc (3 × 50 mL), and the combined organic fraction dried and the solvent evaporated to give alcohol 2-(2-hydroxyethyl)-2,3-dihydro-1H-inden-1-ol (2.18 g) as a yellow oil which was used for the next step without further purification. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.43-7.35(m, 1H), 7.26-7.18(m, 3H), 4.9(br d, $J$ = 6.6 Hz, 1H), 3.91-3.73(m, 2H), 3.4(s, 1H), 3.1-2.92(m, 1H), 2.6-2.46(m, 1H), 2.29-2.2(m, 1H), 1.95-1.86(m, 2H).

**4.2.15. 2-(2-hydroxyethyl)-1,2,3,4-tetrahydronaphthalen-1-ol, 13**

Synthesis of intermediate **13** followed the same procedure as **12** above and was used for the next step without further purification.

**4.2.16. 2-(2-iodoethyl)-1*H*-indene, 14**

A solution of triphenylphosphine (5.28 g, 20.2 mmol) and imidazole (1.37 gm, 20.2 mmol) in $CH_2Cl_2$ was cooled to 0 °C, and iodine (5.09 g, 20.15 mmol) was added. The mixture was stirred for 30 min and then a $CH_2Cl_2$ solution (20 mL) of the crude 2-(2-hydroxyethyl)-1*H*-inden-3-ol, **12** (2.18 gm, ~13.43 mmol) obtained above was added in a dropwise manner. The reaction mixture was stirred for 12 h at rt, filtered, the organic layer washed with $H_2O$ and then by aqueous sodium thiosulfate (50 mL), $H_2O$ 950 mL) and brine 950 mL). The organic layer was dried over sodium sulfate, excess solvent removed under reduced pressure and the residue purified on combiflash column using EtOAc/hexane (1:9) as eluent to afford 2-(2-iodoethyl)-1*H*-indene (**14**) as a brown solid. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.4(d, J = 7.5 Hz, 1H), 7.32(d, J = 7.5 Hz, 1H), 7.26-7.21(m, 1H), 7.17-7.11(m, 1H), 6.62(s,1H), 3.4-3.35(m, 4H), 3.11-3.07(m, 2H)

**4.2.17. 3-(2-iodoethyl)-1,2-dihydronaphthalene, 15**

Under the same Appel reaction conditions described for **14** above, the alkylating agent **15** was prepared in 26% yield using 2-(2-hydroxyethyl)-1,2,3,4-tetrahydronaphthalen-1-ol,**13** as the precursor. $^1$H NMR

(300 MHz, $CDCl_3$): δ 7.15-7.1(m, 3H), 7.03-7.0(m, 1H), 6.28(s, 1H), 3.31(t, *J* = 7.8 Hz, 2H), 2.86-2.75(m, 4H), 2.27(t, *J* = 8.4, 2H).

**4.2.18. 2-(2-(1H-inden-2-yl)ethyl)-1,2,3,4-tetrahydroisoquinoline, 2a**

Using method **B**, the alkylating agent 2-(2-iodoethyl)-1*H*-indene (**11**) was used to alkylate THIQ (section **4.1.2**) to afford compound **2a** as a white solid in 29% yield. Mp: 87-89 $^oC$, $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.38 (d, 1H, *J* = 7.2 Hz), 7.29-7.19 (m, 2H), 7.15-7.02 (m, 5H), 6.59 (s, 1H), 3.74 (s, 2H), 3.38 (s, 2H), 2.95 (t, *J* = 6.0 Hz, 2H), 2.83 (s, 6H). Anal. calc for $C_{20}H_{21}N$: C 87.23, H 7.69, N 5.09; Found: C 86.97, H 7.74, N 4.99.

**4.2.19. 2-(2-(3,4-Dihydronaphthalen-2-yl)ethyl)-1,2,3,4-tetrahydroisoquinoline, 2b**

Using the alkylating agent **12**, THIQ was alkylated under the general alkylation method **B** to produce compound **2b** as a hygroscopic solid in 35% yield, $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.18-6.96 (m, 8H), 6.29(s, 1H), 3.7(s, 2H), 2.93(t, *J* = 6 Hz, 2H), 2.86-2.77(m, 4H), 2.76-2.68(m, 2H), 2.51(t, *J* = 8.7 Hz, 2H), 2.31(t, *J* = 8.1 Hz, 2H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 140.18, 134.74, 134.39, 134.23, 128.66, 127.18, 126.6, 126.42, 126.2, 126.12, 125.6, 125.38, 123.4, 56.92, 56.16, 51.02, 35.41, 29.14, 28.15, 27.58. Anal. calcd. for $C_{21}H_{23}N$ : C 87.15, H 8.01, N 4.84 ; Found: 87.04, 7.96, 4.78.

**4.2.20. 4,4'-(4-Chlorobut-1-ene-1,1-diyl)bis(chlorobenzene), 19**

To a solution of 4-chlorobutyryl chloride (5 mL, 44 mmol) in dry THF (50 mL) was added dropwise to a solution of 4-chlorophenylmagnesium bromide (100 mL, 1.0 M in $Et_2O$, 100 mmol) at -5 °C in 1 hr. After addition was complete, the reaction mixture was stirred at rt overnight, and then quenched with saturated $NH_4Cl$ solution followed by extraction with EtOAc (400 mL). The organic layer was separated and washed with brine (2 x 200 mL), then dried with anhydrous $Na_2SO_4$ and filtered. The filtrate was concentrated in vacuo, and the residue purified directly on silica gel using flash chromatography to give the pure product, 4,4'-(4-chlorobut-1-ene-1,1-diyl)bis(chlorobenzene) (**19**), 9.3 g, yield 68%. $^1H$ NMR (300MHz, $CDCl_3$): 7.36 (d, *J* = 6.0 Hz, 2H), 7.24 (d, *J* = 6.6 Hz, 2H), 7.12 (d, *J* = 6.0 Hz, 2H), 7.09 (d, *J* = 6.0 Hz, 2H), 6.10 (t, *J* = 7.2 Hz, 1H), 3.57 (t, *J* = 6.6 Hz, 2H), 2.56 (m, 2H).

**4.2.21. 2-(4,4-Bis(4-chlorophenyl)but-3-en-1-yl)-1,2,3,4-tetrahydroisoquinineol hydrobromide, 2c**

Compound **2c** was prepared by reacting the alkylation agent 4,4'-(4-chlorobut-1-ene-1,1-diyl)bis(chlorobenzene) (**19**) and THIQ under the general alkylation **B** conditions to afford **2c** in 56% yield. Mp 215-216 °C ,$^1H$ NMR (DMSO-$d_6$): 9.69 (brs,1H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.15-7.28 (m, 8H), 6.18 (t, *J* = 7.5 Hz, 1H), 4.46-4.50 (m, 1H), 4.23-4.31 (m ,1H), 3.61-3.66 (m, 1H), 3.30-3.38 (m, 3H), 3.04-3.09 (m, 2H), 2.53-2.58 (m, 2H). Anal. calcd for $C_{25}H_{24}BrCl_2N$: C 61.37, H 4.94, N 2.86. Found: C 61.33, H 5.05, N 2.95.

**4.2.22. 1-(4-bromobutyl)-4,4-dimethylpiperidine-2,6-dione, 21**

A mixture of 4,4-dimethylpiperidine-2,6-dione, **20** (0.93 g, 5 mmol) and 1,4-dibromobutane (5.4 g, 25 mmol) was stirred under reflux in dry $CH_3CN$ (20 mL) for 12 h. The reaction mixture was allowed to cool to room temperature and the excess solvent was removed under reduced pressure. The crude product obtained was directly purified on flash column chromatography (silica gel, ethyl acetate/light petroleum 1:3) to afford 1-(4-bromobutyl)-4,4-dimethylpiperidine-2,6-dione, (**21**) as a colorless oil which was used in the next stage without further purification. $^1H$ NMR (300 MHz, $CDCl_3$): δ 3.8(t, *J* = 7.2, 2H), 3.42(t, *J* = 6.6 Hz, 2H), 2.51(s, 4H), 1.91-1.82 (m, 2H), 1.73-1.62(m, 2H), 1.08(s, 6H).

**4.2.23. 1-(4-(3,4-Dihydroisoquinolin-2(1H)-yl)butyl)-4,4-dimethylpiperidine-2,6-dione hydrochloride, 2d**

Under the general alkylation method **B** described above, the alkylating agent **21** was reacted with THIQ to afford compound **2d** as a highly hydroscopic HCl salt in 76% yield. $^{1}$HNMR (300 MHz, DMSO-$d_6$): δ 9.82 (brs, 1H), 7.66-7.60 (m, 1H), 7.47-7.38 (m, 2H), 7.15(dd, *J* = 5.4, 10.8 Hz,1H), 3.59 (t, *J* = 7.4 Hz, 2H), 3.40 (s, 2H), 2.97 (s, 2H), 2.50 (s, 8H), 1.70-1.60 (m, 2H), 1.35 (t, *J* = 7.5 Hz, 2H), 9.95 (s, 6H). Anal. calcd for $C_{20}H_{29}ClN_2O_2$. 0.15 EtOAc: C; 63.53, H; 7.73, N; 7.41. Found: C; 63.41, H; 8.10, N; 7.02.

**4.2.24. 1-(4-(Isoindolin-2-yl)butyl)-4,4-dimethylpiperidine-2,6-dione, 2e**

Using isoindoline as the amine, compound **2e** was prepared in its free base form similarly to compound **2d** above in 23% yield. Mp: 84-85 $^{o}$C, $^{1}$HNMR (300 MHz, $CDCl_3$): δ 7.18 (s, 4H), 3.83 (s, 4H), 3.81-3.75 (t, *J* = 3.9 Hz, 2H), 2.76-2.71 (t, *J* = 6.9 Hz, 2H), 2.49 (s, 4H), 1.62-1.58 (t, *J* = 7.7 Hz, 4H), 1.06 (s, 6H). Anal calcd for $C_{19}H_{26}N_2O_2$•0.15 $H_2O$: C 71.96, H 8.26, N 8.83. Found: C 71.93, H 8.25, N 8.81.

**4.2.25. Synthesis of compounds 3c-f**

In general, compounds **3c-f** were synthesized following the general alkylation method **A** described above (section **4.1.1**) using the common alkylating agent 4-chloro-1-(4-chlorophenyl)butan-1-one (**22**) to obtain the respective final compounds as HCl salts, except for **3c** which was obtained as a free base (**Scheme 6**).

**4.2.25.1. 1-(4-Chlorophenyl)-4-(3,4-dihydroquinolin-1(2H)-yl)butan-1-one, 3c**

Using 1,2,3,4-tetrahydroquinoline as the amine and 4-chloro-1-(4-chlorophenyl)butan-1-one(**22**) as the alkylating agent, compound **3c** was produced as a white crystalline solid in 33% yield. Mp: 192-193 ºC.$^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 7.97 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.07 – 6.91 (m, 2H), 6.85 (d, 1H), 6.66 (d, 1H), 3.38 – 3.25 (m, 4H), 3.11 (t, *J* = 6.9 Hz, 2H), 2.71 (t, *J* = 6.2 Hz, 2H), 1.97 – 1.83 (m, 4H). $^{13}$C NMR (75MHz, DMSO-$d_6$) δ 198.54, 145.25, 139.46, 135.16, 129.44, 129.22, 128.92, 127.15, 122.34, 115.64, 110.65, 50.64, 49.49, 35.66, 28.15, 22.22, 20.87. Anal. calcd for $C_{19}H_{20}ClNO$: C, 72.72; H, 6.42; N, 4.46. Found: C, 72.48; H, 6.30; N, 4.35.

**4.2.25.2. 1-(4-Chlorophenyl)-4-(2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)butan-1-one hydrochloride, 3d**

Using 2,3,4,5-tetrahydro-1H-benzo[b]azepine as the amine and reacting it with **22**, compound **3d** was obtained as a white crystalline HCl salt. Yield: 35%, mp:192-193 ºC. $^{1}$H NMR (300 MHz, Methanol-$d_4$) δ 7.95 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 7.3 Hz, 1H), 7.54 – 7.35 (m, 5H), 4.86 (t, *J* = 2.6 Hz, 2H), 4.03 – 3.44 (m, 4H), 3.32 – 3.02 (m, 4H), 2.36 – 1.79 (m, 4H). $^{13}$C NMR (75 MHz, $CD_3OD$) δ 197.63, 139.28, 138.80, 136.67, 134.94, 133.19, 130.46, 129.43, 128.59, 127.72, 123.75, 56.70, 52.39, 34.45, 33.51, 25.45, 23.68, 19.47. Anal. calcd for $C_{20}H_{23}Cl_2NO$: C, 65.94; H, 6.36; N, 3.84. Found: C, 65.66; H, 6.41; N, 3.74.

**4.2.25.3. 1-(4-Chlorophenyl)-4-(4,5-dihydro-1H-benzo[c]azepin-2(3H)-yl)butan-1-one hydrochloride, 3e**

Intermediate **22** was used to alkylate the amine 2,3,4,5-tetrahydro-1H-benzo[c]azepine to obtain compound **3e** as a white solid crystal. Yield: 52%, mp: 201-202 ºC. $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ

11.24 (s, 1H), 7.93 (d, *J* = 8.8 Hz, 2H), 7.56 (dd, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 7.3 Hz, 1H), 7.34 – 7.21 (m, 3H), 4.56 (d, *J* = 14.1 Hz, 1H), 4.38 (dd, *J* = 5.1, 14.1 Hz, 1H), 3.52 – 3.42 (m, 2H), 3.35 (s, 2H), 3.12 (td, *J* = 2.4, 6.9 Hz, 2H), 2.88 (t, *J* = 18.8 Hz, 2H), 2.02 (q, *J* = 7.6 Hz, 2H), 1.94 – 1.84 (m, 2H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 198.15, 143.47, 138.59, 135.44, 132.21, 130.48, 130.25, 129.93, 129.62, 129.24, 127.10, 56.85, 55.95, 35.66, 33.38, 22.40, 18.39. Anal. calcd for $C_{20}H_{23}Cl_2NO$: C, 65.94; H, 6.36; N, 3.84. Found: C, 65.67; H, 6.44; N, 3.72.

**4.2.25.4. 1-(4-Chlorophenyl)-4-(4,5-dihydro-1H-benzo[d]azepin-3(2*H*)-yl)butan-1-one hydrochloride, 3f**

Amine 2,3,4,5-tetrahydro-1H-benzo[d]azepine was reacted with **22** to produce compound **3f** as a white solid crystal. Yield: 59%, mp: 240-242 ºC. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.31 (s, 1H), 7.98 (dd, *J* = 8.3 Hz, 2H), 7.59 (dd, *J* = 8.4 Hz, 2H), 7.22 – 7.15 (m, 4H), 3.72 – 3.59 (m, 2H), 3.53 – 3.41 (m, 2H), 3.18 (dt, *J* = 6.6, 14.4 Hz, 4H), 2.95 (dt, *J* = 6.8, 16.9 Hz, 4H), 2.09 (q, *J* = 7.6 Hz, 2H).$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 198.18, 139.80, 138.62, 135.52, 130.28, 129.53, 129.29, 127.40, 56.86, 53.70, 35.87, 31.16, 18.34. Anal. calcd for $C_{20}H_{23}Cl_2NO$: C, 65.94; H, 6.36; N, 3.84. Found: C, 65.83; H, 6.44; N, 3.90.

**4.2.26. 5-(4-Chlorobutanoyl)indolin-2-one, 24**

A modified acylation reaction described by Lackey et al.[31] was followed to access intermediate **3b**. Briefly, to a dry 100 mL round-bottomed flask equipped with a stirrer was added 5 g (37.5 mmol) of $AlCl_3$, 30 mL of carbon disulfide ($CS_2$), and 2.5 mL (22.5 mmol) of 4-chlorobutyryl chloride at 0 ºC with stirring. To the mixture obtained was added 2 g (15 mmol) of oxindole (**23**) in a portionwise manner over 20 minutes. After the addition was completed, the reaction mixture was allowed to warm to rt and stirred overnight to produce a red precipitate. The content was dumped into a beaker containing 100g of ice with 5 mL conc. HCl and stirred thoroughly. The brick red precipitate obtained was dissolved in methanol and loaded onto silica column and subsequently separated by combiflash (gradient elution up to 50% EtOAc in hexanes) to afford 2.6 g (73%) of 5-(4-chlorobutanoyl)indolin-2-one, **24**. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.75 (s, 1H), 7.84 (dd, *J* = 1.9, 8.2 Hz, 1H), 7.78 (s, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 3.68 (t, *J* = 6.7 Hz, 2H), 3.52 (s, 2H), 3.07 (t, *J* = 7.1 Hz, 2H), 2.03 (q, *J* = 6.9 Hz, 2H).$^{13}$C NMR δ 197.83, 177.19, 148.82, 130.53, 129.41, 126.55, 124.52, 109.19, 45.39, 35.95, 35.16, 27.48.

**4.2.27. 5-(4-(3,4-Dihydroisoquinolin-2(1H)-yl)butanoyl)indolin-2-one, 3g**

Using the alkylating agent **24**, THIQ was alkylated under the general alkylation method **A** condition to afford compound **3g** as a free base in 59% yield. Mp: 166-168 ºC. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.23 (s, 1H),7.84 (d, *J* = 4.7 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.16 – 6.96 (m, 4H), 6.85 (s, 1H), 3.61 (s, 2H), 3.51 (s, 2H), 3.02 (t, *J* = 7.2 Hz, 2H), 2.86 (t, *J* = 5.9 Hz, 2H), 2.75 (t, *J* = 5.9 Hz, 2H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.04 (q, *J* = 7.2 Hz, 2H). $^{13}$C NMR (75MHz, $CDCl_3$) δ 199.01, 177.77, 146.77, 134.74, 134.31, 131.90, 129.38, 128.60, 126.55, 126.11, 125.57, 125.34, 124.63, 109.16, 57.34, 55.97, 50.78, 35.97, 35.90, 29.01, 21.92. Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38; Found: C, 75.12; H, 6.74; N, 8.16.

**4.2.28. 2-(2-(3,4-Dihydroisoquinolin-2(1H)-yl)ethyl)-5-fluoro-2,3-dihydro-1H-inden-1-one, 3h**.

Using the previously reported alkylating agent 2-(2-chloroethyl)-5-fluoro-2,3-dihydro-1H-inden-1-one (**25**),[20, 21] THIQ was alkylated under alkylation method **B** to afford compound **3h** in 23% yield. Mp 240-241 ºC; $^1$H NMR (DMSO-$d_6$): 7.73 (dd, *J* = 5.8, 8.4 Hz, 1H), 7.45 (d, *J* = 9.0 Hz, 1H), 7.24 (m, 5H),

4.52 (m, 2H), 4.28 (m, 2H), 3.68 (m, 1H), 3.34 (m, 6H), 2.99 (m,1H), 2.89 (m, 2H), 2.31 (m, 1H), 1.99 (m, 1H). Anal. calcd for $C_{20}H_{21}ClFNO$: C 69.46, H 6.12, N 4.05; Found: C 69.18, H 6.08, N 4.60.

**4.2.29. 2-(2-(3,4-Dihydroisoquinolin-2(1H)-yl)ethyl)-2,3-dihydro-1H-inden-1-one hydrochloride, 3i**
Under the general alkylation method **B**, the previously described alkylating agent 2-(2-chloroethyl)-2,3-dihydro-1H-inden-1-one (**26**)[20] was coupled to THIQ to afford compound **3i** as the HCl salt in 65% yield. Mp: 201-203 ºC. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.18 (s, 1H), 7.74 – 7.63 (m, 2H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.48 – 7.40 (m, 1H), 7.29 – 7.15 (m, 4H), 4.49 (s, 1H), 4.31 (s, 1H), 3.68 (s, 1H), 3.40 (t, *J* = 8.4 Hz, 3H), 3.01 (s, 1H), 2.92 (d, *J* = 4.1 Hz, 1H), 2.89 – 2.77 (m, 2H), 2.41 – 2.28 (m, 1H), 1.99 (d, *J* = 9.8 Hz, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 207.35, 154.03, 136.27, 135.65, 131.92, 128.97, 128.07, 128.00, 127.38, 127.04, 123.76, 53.85, 52.05, 49.10, 44.65, 32.59, 25.42. Anal. Calcd for $C_{20}H_{22}ClNO{\cdot}0.2H_2O$: C, 72.47; H, 6.81; N, 4.23. Found: C, 72.55; H, 6.56; N, 4.29.

**4.2.30. 5-Chloro-2-(2-(3,4-dihydroisoquinolin-2(1H)-yl)ethyl)-2,3-dihydro-1H-inden-1-one hydrochloride, 3j**.
The previously reported alkylating agent **27**[20] was reacted with THIQ under the general alkylation method **B** condition to afford compound **3j** as the HCl salt in 41% yield. Mp 239-240 °C, $^1$H NMR (DMSO-$d_6$): 11.10 9 (brs,1H), 7.72 (s,1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.17-7.27 (m, 4H), 4.51 (d, *J* = 12.6 Hz, 1H), 4.25-4.32 (m,1H), 3.65-3.2 (m,1H), 3.23-3.42 (m, 5H), 2.92-3.02 (m,1H), 2.86-2.92 (m, 2H), 2.29-2.37 (m,1H), 1.95-2.05 (m,1H).Anal. calcd for $C_{20}H_{21}Cl_2NO$: C 66.30, H 5.84, N 3.87. Found: C 66.29, H 5.94, N 3.93.

**5. Receptor binding studies**
Binding affinities reported in **Tables 1- 3** were conducted by the National Institute of Mental Health Psychoactive Drug Screening Program (NIMH-PDSP). Details of the methods and radioligands used for the binding assays were previously reported.[32]

**Acknowledgements**
This work was supported by the continuing financial support of the NIH/NIGMS SCORE grant number 2SC1GM116724, NIMHD RCMI grant number G12 RR 03020 and a Title III Grant to Florida A&M University. The work was also supported in part by the Pharmaceutical Research Center NIH/ NCRR 1C06-RR12512-01 Grant. Ki determinations and receptor binding profiles were generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract # HHSN-271-2013-00017-C (NIMH PDSP). The NIMH PDSP is directed by Bryan L. Roth, MD, PhD, at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscoll at NIMH, Bethesda MD, USA. Funding sources acknowledged had no involvement in the study design, data collection and interpretation, or article preparation and submission of this manuscript.

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**Synthesis and evaluation of the structural elements in alkylated tetrahydroisoquinolines for binding to CNS receptors**

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**Graphical Abstract:**