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# SYNTHESIS OF NOVEL PYRIMIDO[4,5-*c*]PYRIDAZINES AND 1,2-DIHYDRO-3a,7,9,9b-TETRAAZA-CYCLOPENTA[a]NAPHTHALEN-3-ONES AS POTENT INHIBITORS OF LYMPHOCYTE SPECIFIC KINASE (LCK)

**John C. VanRens, Mark Sabat,* Todd A. Brugel, Jennifer Maier, Matthew J. Laufersweiler, Adam Golebiowski, Steve Berberich, and Biswanath De**

P&G Pharmaceuticals, Health Care Research Center, 8700 Mason-Montgomery Rd, Mason, OH 45040, USA. E-mail address: sabat.mp@pg.com.

**Abstract**– This paper details the synthesis of a novel class of 1,2-dihydro-pyrimido[4,5-*c*]pyridazines and substituted 1,2-dihydro-3a,7,9,9b-tetraaza-cyclopenta[a]naphthalen-3-one. The most potent analogs disclosed showed low nanomolar activity for the inhibition of lck kinase.

## INTRODUCTION

In our search for potent inhibitors of Lymphocyte Specific Kinase (lck)[1] we examined a series of pyridazine derivatives as potential scaffolds for the design of kinase inhibitors. This article details the synthetic methodology developed by our research team to access a novel class of bi- and tri-cyclic pyridazine derivatives including the initial lead compound (**1a**) and a more advanced analog (**2**). Pyridazines and their derivatives have been used for the development of various chemical agents[2] and potential therapeutics including kinase inhibitors.[3] Various synthetic routes are available to obtain simple pyridazine analogs, however the heterocyclic core structure found in the lead molecules (**1a** & **b**) has been rarely described.[4a,b] No literature reference was found detailing derivatives which contain a 3-aryl and 7-anilino group attached to the central ring system. Additionally the core structure of the tricyclic compound (**2**) has not been previously described.

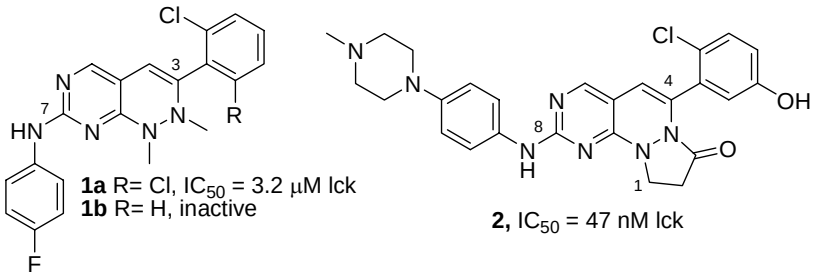
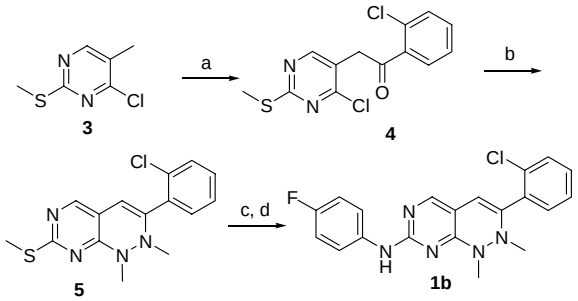



**Figure 1**. Initial lead compound (**1**) and advanced analog (**2**).

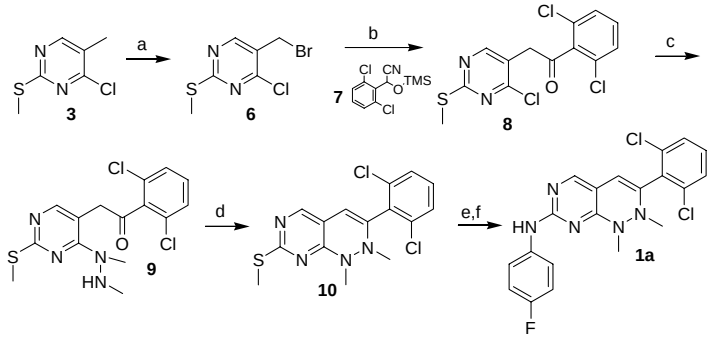
## RESULTS AND DISCUSSION

Our initial route toward the successful synthesis of pyridazine (**1a**) started with the exploration of conditions to synthesize the inactive model compound (**1b**). This analog contained a single Cl- substituent on the C-3 phenyl group and could be assembled directly using 4-chloro-5-methyl-2-methylsulfanyl pyrimidine[5] (**3**) (**Scheme 1**). Deprotonation of the 5-methyl group with LiHMDS and addition to methyl-2-chlorobenzoate gave ketone (**4**). Treatment of this key intermediate with 1,2-dimethyl hydrazine hydrochloride in the presence of Hünig's base gave pyridazine (**5**). Oxidation of the thio-methyl moiety of this compound with *m*-CPBA afforded the corresponding sulfoxide which was used without further purification. Nucleophilic addition of 4-fluoroaniline to this material generated the desired final compound (**1b**) in modest yield.



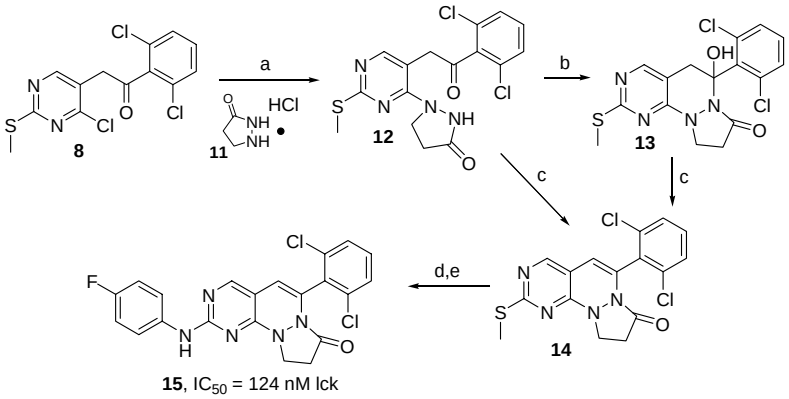

**Scheme 1**. Reagents: a) methyl 2-chlorobenzoate, LiHMDS, THF, 27%; b) 1,2-dimethylhydrazine, Hünig's base, THF, reflux, 55%; c) *m*-CPBA, DCM, 0°C, 88%; d) 4-fluoroaniline, 120°C, 37%.

Extension of this synthetic methodology toward the 2,6-dichlorophenyl C-3 substituted analog (**1a**) however failed as addition of deprotonated **3** to methyl-2,6-dichlorobenzoate was unsuccessful. An alternative methodology toward these analogs was devised and is described in **Scheme 2**. Pyrimidine (**3**) was brominated with *N*-bromosuccinimide in the presence of catalytic benzoyl peroxide[6] and the resulting benzylbromide (**6**) was treated with the anion of cyanohydrin (**7**) (generated from the corresponding aldehyde with TMSCN and $ZnI_2$)[6] to yield ketone (**8**). Compound (**8**) was further reacted with *N*,*N*-dimethylhydrazine in the presence of Hünig's base, to give adduct (**9**). Treatment of this material with 1 N HCl solution gave the cyclized analog (**10**). Oxidation with *m*-CPBA and displacement with 4-fluoroaniline afforded the lead molecule (**1a**).



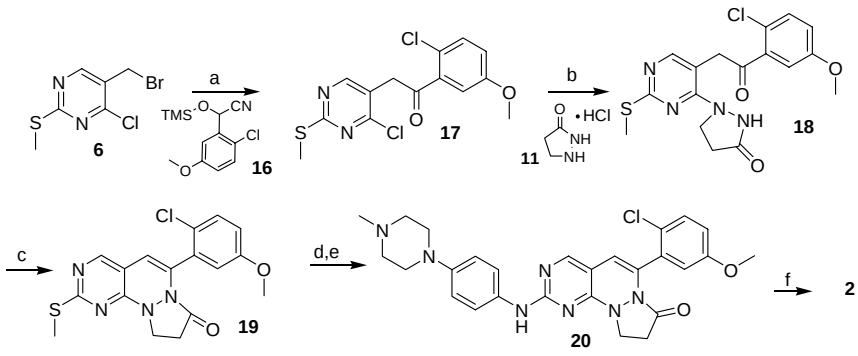

**Scheme 2**. Reagents: a) *N*-bromosuccinimide, cat. benzoyl peroxide, 1,2-dichloroethane, Δ, 66%; b) LDA, THF, -78°C, 39%; c) 1,2-dimethylhydrazine hydrochloride, Hunig's base, DMF, 32% d) 1 N HCl, EtOH, quant yield; e) *m*-CPBA, DCM, 91%, f) 4-fluoroaniline, NMP, 100°C, 32%

The modest biological activity (lck $IC_{50}$ = 3.2 μM) of pyridazine (**1a**) led us to investigate the synthesis of tricyclic variants of these molecules. We believed that this change would rigidify the core structure, allow for a better interaction with the active site of lck, and result in greater potency.[7] These analogs were constructed by the addition of tetrahydro-3*H*-pyrazol-3-one (**11**)[8] to ketone (**8**) to give intermediate (**12**) (**Scheme 3**). Initial attempts to cyclize this material with 1 N HCl solution gave no evidence of reaction. Treatment of this adduct with conc. HCl generated the cyclic aminal **(13**) (isolated as a stable solid product). Exposure of aminal (**13**) to *p*-TsOH in refluxing toluene (using a Dean-Stark trap to remove the eliminated water) gave the desired product (**14**) after 4 h of vigorous reflux. Product (**14**) could be made directly from compound (**12**) using the above described reaction conditions (cyclization and elimination occurring in one pot). Oxidation of intermediate (**14**) with Oxone® and displacement with 4-fluoroaniline gave compound (**15**). This tricyclic pyridazine derivative displayed greatly improved biological activity (lck $IC_{50}$ = 124 nM).




**Scheme 3**. Reagents: a) Hunig's base, DMF, 80°C; b) conc. HCl, EtOH, Δ, 22%; c)*p*-TsOH, toluene, Dean Stark trap 130°C, 61%; d) Oxone,® THF, $H_2O$, 51%; e) 4-fluoroaniline, NMP, 100°C, 33%

Subsequent exploration of the SAR at the C-4 position of this tricyclic core structure ultimately resulted in the advanced analog (**2**) which possessed greatly improved biological activity (lck $IC_{50}$ = 47 nM). The synthetic route used to access this compound containing a 2-chloro-5-hydroxy phenyl group at the C-4-position is described in **Scheme 4**. This analog required the use of 2-(2-chloro-5-methoxyphenyl)-2-(trimethylsilyloxy)acetonitrile (**16**) (formed by analogy to **Scheme 2** from 2-chloro-5-methoxybenzaldehyde[9]) which was deprotonated with LDA and treated with the α-bromo pyrimidine (**6**) to form ketone (**17**). This material was treated as before (**Scheme2**) to generate compound (**19**). Oxidation of the thiomethyl group followed by nucleophilic addition of 4-(4-methylpiperazino)aniline gave desired material (**20**) which was then treated with $BBr_3$ to give the most advanced analog (**2**) in this series.



**Scheme 4**. Reagents: a) LDA, THF, -78°C, 21%; b) Hünig's base, DMF, 80°C, 95%; c) *p*-TsOH, toluene, Dean-Stark trap, 130°C, 79%; d) Oxone,® THF, $H_2O$, 25%; e) 4-(4-methylpiperazino)-aniline, neat, MW, 150°C, 22%; f) $BBr_3$, DCM, -78°C, 54%.

In summary we have described the design, and synthesis of two novel classes of heterocycles: the 1,2-dihydropyrimido[4,5-*c*]pyridazines and their tri-cyclic variants the 1,2-dihydro-3a,7,9,9b-tetraaza-cyclopenta[a]naphthalen-3-ones. SAR studies around compound (**2**) which identified other low nanomolar lck inhibitors will be disclosed in a subsequent publication.[7]

## EXPERIMENTAL

**2-(4-Chloro-2-(methylthio)pyrimidin-5-yl)-1-(2-chlorophenyl)ethanone (4):** Compound (**3**) (1.0 g, 5.7 mmol) was dissolved in THF (30 mL) and stirred at rt under $N_2$. LiHMDS in THF (5.7 mL, 1.0 M solution, 5.7 mmol) was added slowly to the stirred solution. After 15 min, methyl 2-chlorobenzoate (0.97 g, 5.7 mmol) was added to the mixture. After 1 h, additional LiHMDS (14.3 mL, 14.3 mmol) was added and the reaction mixture was stirred at rt overnight. The mixture was then diluted with $H_2O$ (100 mL) and extracted with EtOAc (3 x 150 mL). The combined organic fractions were dried over $Na_2SO_4$ and concentrated. The crude residue was purified on a Biotage Flash 40M column eluted with 10-15% EtOAc/hexane. The product was obtained as yellow solid (0.48 g, 27% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.30-7.42 (m, 4H), 4.22 (s, 2H), 2.56 (s, 3H); ESI/MS: 313.2 (M+H).

**3-(2-Chlorophenyl)-1,2-dimethyl-7-(methylthio)-1,2-dihydropyrimido[4,5-*c*]pyridazine (5):** To a solution of compound (**4**) (0.25 g, 0.80 mmol) in THF (5 mL) was added *N*, *N*-diisopropylethylamine (2 mL) and *N*, *N*'-dimethylhydrazine hydrochloride (0.21 g, 1.60 mmol) and the mixture was refluxed overnight. The cooled reaction mixture was diluted with 1 N HCl (75 mL) and extracted with EtOAc (3 x 100 mL). The combined organic fractions were dried over $Na_2SO_4$ and concentrated. The crude residue was purified on a Biotage Flash 40S column eluting with 10% EtOAc/hexane. The product was obtained as yellow oil (0.14 g, 55% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.26-7.37 (m, 4H), 6.30 (s, 1H), 3.31 (s, 3 H), 2.55 (s, 6H); ESI/MS: 319.1 (M+H).

**3-(2-Chlorophenyl)-1,2-dimethyl-7-(methanesulfinyl)-1,2-dihydropyrimido[4,5-*c*]pyridazine (Scheme 1 step c):** Compound (**5**) (0.14 g, 0.44 mmol) was dissolved in $CH_2Cl_2$ (5 mL) and cooled to 0°C under $N_2$. To this solution was added *m*-CPBA (0.10 g, 0.57 mmol) and the reaction was stirred for 1 h. The mixture was diluted with saturated aq. $NaHCO_3$ solution (50 mL) and extracted with $CH_2Cl_2$ (2 x 100 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated. The product was obtained as orange foam (0.13 g, 88.2% yield). This material was used without further purification. ESI/MS: 335.1 (M+H).

**3-(2-Chlorophenyl)-*N*-(4-fluorophenyl)-1,2-dimethyl-1,2-dihydropyridazino[3,4-*d*]pyrimidin-7-amine (1b):** The previous sulfoxide (**3-(2-chlorophenyl)-1,2-dimethyl-7-(methanesulfinyl)-1,2-dihydropyrimido[4,5-*c*]pyridazine)** (0.13 g, 0.39 mmol) and 4-fluoroaniline (0.56 g, 5.84 mmol) were combined and heated to 120°C for 4 h. LC/MS indicated complete reaction and the mixture was cooled and the residue was purified with preparative HPLC. The product was obtained as yellow solid (0.055 g, 37% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1 H), 7.56-7.62 (m, 3 H), 7.43-7.46 (m, 2 H), 7.27-7.33 (m, 2 H), 7.05 (t, *J* = 8.7 Hz, 2 H), 6.36 (s, 1 H), 3.35 (s, 3 H), 2.64 (s, 3 H). HRMS (FAB) calcd. for $C_{20}H_{17}N_5ClF$ 381.1156, found 382.1236.

**5-Bromomethyl-4-chloro-2-(methylthio)pyrimidine (6):** To a solution of compound (**3**) (1.0 g, 5.7 mmol) in 1,2-dichloroethane (25 mL) was added *N*-bromosuccinimide (1.1 g, 6.3 mmol) and then benzoyl peroxide (0.14 g, 0.57 mmol). The reaction mixture was heated to reflux under $N_2$ atmosphere for 2 h. The crude reaction mixture was cooled, diluted with $H_2O$ (100 mL) and extracted with $CH_2Cl_2$ (2 x 150 mL). The combined organics were dried over $MgSO_4$ and concentrated. The crude residue was purified on a Biotage Flash 40M column eluted with 10-20% EtOAc/hexane. The product was obtained as a yellow oil (0.95 g, 66% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1 H), 4.51 (s, 2 H), 2.62 (s, 3 H); ESI/MS: 254.5 (M+H).

**2-(4-Chloro-2-methylsulfanylpyrimidin-5-yl)-1-(2,6-dichlorophenyl)ethanone (8):** Compound (**6**) (9.9 g, 36 mmol) was taken up in THF (110 mL) and cooled to -78°C in a dry ice/acetone bath. A soln of LDA (20 mL, 1.8 M in THF/heptane/ethylbenzene, 36 mmol) was added slowly over 20 min to the cooled reaction mixture. To this solution was then added **2-(2,6-dichlorophenyl)-2-(trimethylsilyloxy)acetonitrile (7)**[6] (6.4 g, 25 mmol) dissolved in THF (20 mL) and the mixture was stirred at -78°C for 2 h. The reaction was warmed to rt, diluted with $H_2O$ (300 mL) and concentrated to remove most of the THF. The concentrated slurry was extracted with EtOAc (3 x 300 mL) and the combined organics were dried over $Na_2SO_4$ and stripped of solvent. The crude residue was purified by flash column chromatography eluted with 10-20% EtOAc/hexanes. The product was obtained as yellow oil (3.4 g, 39% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.30-7.40 (m, 3 H), 4.24 (s, 2 H), 2.58 (s, 3 H). *Anal.* Calcd for $C_{13}H_9N_2OCl_2S$: C, 44.91; H, 2.61; N, 8.06. Found: C, 44.54; H, 2.61; N, 8.20; ESI/MS: 348.6 (M+H).

**3-(2,6-Dichlorophenyl)-1,2-dimethyl-7-methylsulfanyl-1,2-dihydropyrimido[4,5-*c*]pyridazine (10):** To a stirred solution of compound (**8**) (0.12 g, 0.35 mmol) in DMF (4 mL), was added *N*,*N*-diisopropylethylamine (0.07 mL, 0.38 mmol) and *N*,*N*'-dimethylhydrazine hydrochloride (0.05 g, 0.38 mmol). The resulting mixture was heated at 100°C for 2 h and subsequently cooled, diluted with $H_2O$ (40 mL) and extracted with EtOAc (3 x 75 mL). The combined organics were washed with brine, dried over $Na_2SO_4$ and concentrated. The crude residue was purified with preparative HPLC. The isolated material was the ring open intermediate (**9**) (0.04 g). This material was immediately dissolved in EtOH, to which was added HCl (1 N solution, 1 mL). The mixture was heated to 60°C for 2 h, cooled and concentrated to give the product as orange solid (0.04 g, 32% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1 H), 7.28-7.37 (m, 3 H), 6.14 (s, 1 H), 3.34 (s, 3 H), 2.62 (s, 6 H); ESI/MS: 354.3(M+H).

**3-(2,6-Dichlorophenyl)-1,2-dimethyl-7-(methanesulfinyl)-1,2-dihydropyrimido[4,5-*c*]pyridazine and 3-(2,6-dichlorophenyl)-1,2-dimethyl-7-(methylsulfonyl)-1,2-dihydropyrimido[4,5-c]pyridazine**: Compound (**10**) (0.035 g, 0.10 mmol) was dissolved in $CH_2Cl_2$ (2 mL) and cooled to 0°C under $N_2$. To this soln was added *m*-CPBA (3-chloroperbenzoic acid, 0.04 g, 0.20 mmol) and the reaction was stirred for 1 h at which point LC/MS analysis indicated a complete reaction. The mixture was diluted with saturated aq. $NaHCO_3$ (50 mL) and extracted with $CH_2Cl_2$ (2 x 50 mL). The combined organic layers

were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was obtained as orange foam (0.035 g, 91% yield) was used in the next step without further purification. ESI/MS: 369.3 & 386.3 (M+H).

**[3-(2,6-Dichlorophenyl)-1,2-dimethyl-1,2-dihydropyrimido[4,5-*c*]pyridazin-7-yl](4-fluoro-phenyl)-amine (1a):** To a stirred solution of sulfoxide/sulphone mixture (0.035 g, 0.09 mmol) in NMP (2 mL) was added 4-fluoroaniline (0.2 mL, 2.1 mmol). The mixture was heated to 100°C for 2 h and subsequently cooled to rt. The crude residue was purified with preparative HPLC. The product was obtained as yellow solid (0.012 g, 32% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1 H), 7.59 (dd, *J* = 4.8 Hz, 9.0 Hz, 2 H), 7.39-7.42 (m, 2 H), 7.21-7.27 (m, 1 H), 7.19 (br s, 1 H), 7.05 (t, *J* = 8.7 Hz, 2 H), 6.14 (s, 1 H), 3.34 (s, 3 H), 2.70 (s, 3 H); ESI/MS: 417.3 (M+H).

**1-{5-[2-(2,6-Dichlorophenyl)-2-oxoethyl]-2-methylsulfanylpyrimidin-4-yl}pyrazolidin-3-one (12):** To a solution of compound (**8**) (2.0g, 5.76 mmol) in DMF (20 mL) was added tetrahydro-3*H*-pyrazol-3-one hydrochloride (**11**) (1.06 g, 8.63 mmol) and *N*,*N*-diisopropylethylamine (4.1 mL, 23.0 mmol) and the reaction was heated to 80°C for 3 h. The resulting mixture was cooled, diluted with $H_2O$ (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated. The crude product (2.1 g) was obtained as a brown oil residue and used in the next step without further purification. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1 H), 7.33-7.38 (m, 3 H), 4.25 (t, *J* = 8.4 Hz, 2 H), 4.19 (s, 2 H), 2.77 (t, *J* = 8.4 Hz, 2 H), 2.53 (s, 3 H); ESI/MS: 397.0 (M+H).

**4-(2,6-Dichlorophenyl)-4-hydroxy-8-methylsulfanyl-1,2,4,5-tetrahydro-3a,7,9,9b-tetraazacyclopenta[a] naphthalen-3-one (13):** Compound (**12**) (0.09 g, 0.23 mmol) was dissolved in EtOH (5 mL) to which was added conc. HCl solution (37% aqueous, 3 mL). The mixture was heated to reflux for 30 min. Analysis with LC/MS indicated product formation. The mixture was then concentrated and purified by preparative HPLC to give (0.02 g, 22% yield) of product. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1 H), 7.39-7.42 (m, 2 H), 7.27-7.32 (m, 1 H), 4.37 (t, *J* = 7.2 Hz, 2 H), 3.69 (s, 2 H), 2.87 (t, *J* = 7.2 Hz, 2 H), 2.57 (s, 3 H); ESI/MS: 397.0 (M+H).

**4-(2,6-Dichlorophenyl)-8-methylsulfanyl-1,2-dihydro-3a,7,9,9b-tetraazacyclopenta[a]naphthalen-3-one (14):** Compound (**12**) (2.1 g, 5.0 mmol) was taken up in toluene (30 mL) in a 100 mL round bottom flask. To this mixture was added *p*-TsOH monohydrate (3.8 g, 20.1 mmol) and the reaction was fitted with a Dean-Stark trap containing molecular sieves. The mixture was heated to a vigorous reflux for 4 h, and cooled, diluted with $H_2O$ (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated. The product was obtained as brown oil (1.8 g) and used without further purification in the next step. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.55 (s, 1 H), 7.36-7.39 (m, 2 H), 7.25-7.30 (m, 1 H), 5.58 (s, 1 H), 4.00 (t, *J* = 8.7 Hz, 2 H), 2.76 (t, *J* = 8.7 Hz, 2 H), 2.54 (s, 3 H); ESI/MS: 380.0 (M+H).

**4-(2,6-Dichlorophenyl)-8-methanesulfinyl-1,2-dihydro-3a,7,9,9b-tetraazacyclopenta[a]naphthalen-3-one (Scheme 3 step d):** Compound (**14**) (0.10 g, 0.27 mmol) is dissolved in THF (2 mL) and stirred at rt. To this solution was added dropwise a solution of Oxone® (0.17 g, 0.27 mmol) dissolved in $H_2O$ (2 mL). After 1 h a mixture of sulfoxide/sulfone was formed (2.5:1, analysis by LC/MS). The reaction mixture was diluted with saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organics were washed with brine, dried over $Na_2SO_4$ and concentrated. The crude residue was purified by flash column chromatography eluting with 5% MeOH/EtOAc. The sulfoxide product was isolated as an orange solid (0.055g, 51% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1 H), 7.37-7.40 (m, 2 H), 7.27-7.33 (m, 1 H), 5.41 (s, 1 H), 3.98 (t, *J* = 8.7 Hz, 2 H), 3.24 (s, 3 H), 2.78 (t, *J* = 8.7 Hz, 2 H); ESI/MS: 396.3 (M+H).

**4-(2,6-Dichlorophenyl)-8-(4-fluorophenylamino)-1,2-dihydro-3a,7,9,9b-tetraazacyclopenta[a]naphthalen-3-one (15):** To a stirred solution of the above sulfoxide (0.035g,0.09 mmol) in NMP (1 mL), was added 4-fluoroaniline (0.09 g, 0.9 mmol) and the mixture was heated to 100°C under $N_2$ for 2 h. The reaction was allowed to cool to rt and the crude material was purified by preparative HPLC. The product was obtained as a yellow solid (0.013 g, 33% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.24-7.55 (m, 7 H), 7.06 (t, *J* = 8.7 Hz, 2 H), 5.68 (s, 1 H), 4.01 (t, *J* = 8.7 Hz, 2 H), 2.78 (t, *J* = 8.7 Hz, 2 H); ESI/MS: 443.3 (M+H).

**1-(2-Chloro-5-methoxyphenyl)-2-(4-chloro-2-methylsulfanylpyrimidin-5-yl)ethanone (17):** By a procedure identical to the method used for the synthesis of compound (**8**) with **2-(2-chloro-5-methoxyphenyl)-2-(trimethylsilyloxy)acetonitrile (16)** (prepared from 2-chloro- 5-methoxybenzaldehyde).[8] $^1$H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1 H), 7.37 (d, *J* = 9.0 Hz, 1 H), 7.10 (d, *J* = 3.0 Hz, 1 H), 7.00 (dd, *J* = 3.0, 9.0 Hz, 1 H), 4.36 (s, 2 H), 3.85 (s, 3 H), 2.60 (s, 3 H). ESI/MS: 343.2 (M+H).

**1-{5-[2-(2-Chloro-5-methoxyphenyl)-2-oxoethyl]-2-methylsulfanylpyrimidin-4-yl}pyrazolidin-3-one (18):** By a procedure identical to the method used for the synthesis of compound (**12**). $^1$H NMR (300 MHz, $CD_3OD$) δ 7.90 (s, 1 H), 7.52 (d, *J* = 3.3 Hz, 1 H), 7.32 (d, *J* = 8.7 Hz, 1 H), 6.93 (dd, *J* = 3.3, 8.7 Hz, 1 H), 4.89 (s, 2 H), 4.27-4.34 (m, 1 H), 3.88-4.12 (m, 1 H), 3.86 (s, 3 H), 2.90-2.99 (m, 1 H), 2.63-2.77 (m, 1 H), 2.59 (s, 3 H). ESI/MS: 393.9 (M+H).

**4-(2-Chloro-5-methoxyphenyl)-8-methylsulfanyl-1,2-dihydro-3a,7,9,9b-tetraazacyclopenta[a]naphthalen-3-one (19):** By a procedure identical to the method used for the synthesis of compound (**14**). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1 H), 7.27-7.34 (m, 1 H), 6.85-6.91 (m, 2 H), 5.78 (s, 1 H), 4.07 (t, *J* = 8.7 Hz, 2 H), 3.82 (s, 3 H), 2.74 (t, *J* = 8.7 Hz, 2 H), 2.52 (s, 3 H). ESI/MS: 375.8 (M+H).

**4-(2-Chloro-5-methoxyphenyl)-8-methanesulfinyl-1,2-dihydro-3a,7,9,9b-tetraazacyclopenta[a]naphthalen-3-one (Scheme 4 step d):** By a procedure identical to the method used for the synthesis of compound in **Scheme 3 step d**. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1 H), 7.27-7.32 (m, 1 H), 6.86-6.92 (m, 2 H), 5.67 (s, 1 H), 4.06 (t, *J* = 8.7 Hz, 2 H), 3.83 (s, 3 H), 2.91 (s, 3 H), 2.78 (t, *J* = 8.7 Hz, 2 H). ESI/MS: 391.8 (M+H).

**4-(2-Chloro-5-methoxyphenyl)-8-[4-(4-methylpiperazin-1-yl)-phenylamino]-1,2-dihydro-3a,7,9,9b-tetraazacyclopenta[a]naphthalen-3-one (20):** The sulfoxide compound from the above step (0.05 g, 0.13 mmol) and 4-(4-methyl piperazin-1-yl)aniline (0.24 g, 1.3 mmol) were combined and heated to 140°C with stirring. After 2 h, the mixture was allowed to cool to rt and the crude mixture was purified by preparative HPLC. The product was obtained as an orange solid (0.015g, 22% yield). $^1$H NMR (300 MHz, $CD_3OD$) δ 7.53-7.57 (m, 2 H), 7.41 (s, 1 H), 7.38 (br s, 1 H), 7.11-7.20 (m, 4 H), 7.23-7.27 (m, 1 H), 5.67 (s, 1 H), 4.11 (t, *J* = 8.7 Hz, 2 H), 3.88-3.97 (m, 4 H), 3.54-3.63 (m, 4H), 3.34 (s, 3 H), 3.08 (s, 3 H), 2.84 (t, *J* = 8.7 Hz, 2 H). ESI/MS: 519.0 (M+H).

**4-(2-Chloro-5-hydroxyphenyl)-8-[4-(4-methylpiperazin-1-yl)phenylamino]-1,2-dihydro-3a,7,9,9b-tetraazacyclopenta[a]naphthalen-3-one (2):** To a solution of the above compound (**20**) (0.14 g, 0.27 mmol) in $CH_2Cl_2$ (4 mL) at -78°C, was added $BBr_3$ (1 mL, 1.0 M in $CH_2Cl_2$, 2.7 mL, 2.7 mmol). The mixture was removed from the bath and allowed to warm to rt for 2 h and quenched with MeOH (5 mL). This crude mixture was then brought to pH 7 with saturated aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$ (2 x 50 mL). The combined organics were washed with brine, dried over $Na_2SO_4$ and concentrated. The crude material was purified by preparartive HPLC to give the product (0.07 g, 54% yield) $^1$H NMR (300 MHz, $CD_3OD$) δ 7.43-7.48 (m, 2 H),

7.41 (s, 1 H), 7.38 (br s, 1 H), 7.11-7.20 (m, 4 H), 7.00-7.04 (m, 1 H), 5.67 (s, 1 H), 4.11 (t, *J* = 8.7 Hz, 2 H), 3.84-3.96 (m, 4 H), 3.56-3.66 (m, 4H), 3.00 (s, 3 H), 2.86 (t, *J* = 8.7 Hz, 2 H). ESI/MS: 504.0 (M+H).

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