Synthesis of Biologically Active Seven-Membered-Ring Heterocycles

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Abstract: Seven-membered rings that contain one or more heteroatoms are interesting motifs for organic synthesis. In addition to their synthetic interest, they play an important role in industrial and pharmaceutical chemistry with generally increased central nervous system activity when flanked by aromatic rings. Herein we report a brief summary of some key methods of preparation for seven-membered-ring heterocycles and how they have been applied to the synthesis of commercially desirable products. We then detail new methods that we have developed for the synthesis of biologically active compounds containing this motif.

Key words: Heterocycles, fused-ring systems, medicinal chemistry, polycycles, amines

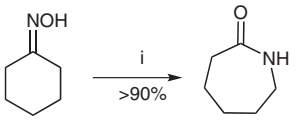
Introduction

Seven-membered-ring heterocycles have found wide spread use in medicinal chemistry due to their diverse biological activity in mammalian systems. In particular, seven-membered-ring heterocycles that are flanked by aromatic rings show interesting activity in the central nervous system.[1] Methods for synthesis of these heterocycles are varied and depend on: (i) the number and type heteroatom to be incorporated in the ring, (ii) the groups attached to the ring, (iii) the degree of unsaturation associated with the seven-membered ring, and (iv) in the case of multiple heteroatom-containing rings, their relationship to one another (1,2-, 1,3-, or 1,4-substitution).[1] Herein we report a brief summary of some key seven-membered-ring heterocyclic compounds and significant methods of synthesis before detailing methods that we have developed for the synthesis of this heterocyclic motif.

Seven-Membered-Ring Heterocycles: Synthesis and Biological Activity

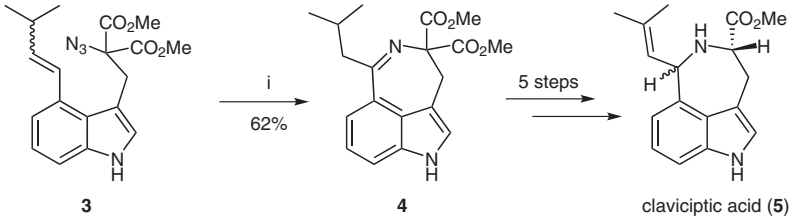
Nitrogen-Containing Seven-Membered Rings

One of the simplest nitrogen-containing heterocycles is caprolactam (**1**, azepan-2-one), which is used industrially for the synthesis of Nylon-6. Approximately two billion tonnes of **1** is produced annually, with the primary method of synthesis involving a Beckman rearrangement of oxime **2**, derived from cyclohexanone (Scheme 1).[2]



Scheme 1 Beckman rearrangement to produce caprolactam (**1**). *Reagents and conditions:* (i) 3.0 M aq H_2SO_4 (0.6 equiv).

The Beckman rearrangement is a commonly employed strategy for the synthesis of other azepanones or azepinones and, through lactam reduction, the corresponding azepanes or azepines.[3] Alternative methods for azepine synthesis include cyclization with an azide and loss of nitrogen to incorporate the nitrogen atom into the seven-membered ring. An illustrative example is shown in Scheme 2, where such a transformation was used to convert azide **3** into imine **4** in a key step for the synthesis of the diastereomeric natural product claviciptic acid (**5**) in a further five steps.[4]



Scheme 2 The key azepine-forming step for the synthesis of claviciptic acid (**5**). *Reagents and conditions:* (i) 1,2-dichlorobenzene, reflux, 3.75 h.

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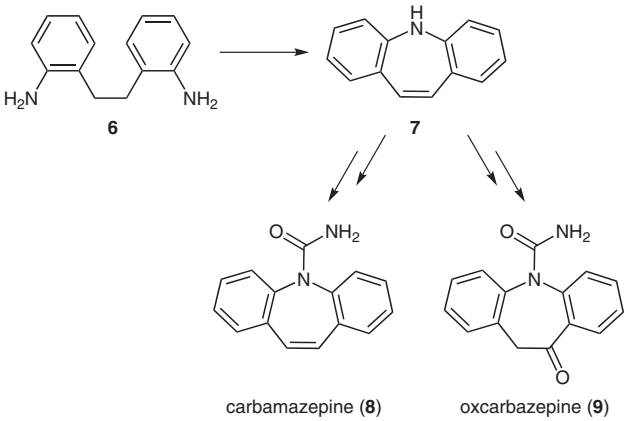
Conversely an appropriately substituted amine can undergo transition-metal-catalyzed intramolecular cross-coupling or ring-closing metathesis to give target azepines.[5]

Chemical modification of parent azepines also allows access to important azepine pharmaceuticals. For example, the dianiline **6** was first used to synthesize dibenzazepine (**7**) in the late 19th century,[6] which in recent times has been used to produce the anticonvulsant drugs carbamazepine (**8**) and oxcarbazepine (**9**) (Scheme 3).[7]

A number of clinically important pharmaceuticals contain seven-membered rings with two nitrogen atoms. The most common of these incorporate the heteroatoms in a 1,4-relationship with an associated aromatic giving rise to 1,4-benzodiazepinones. Examples include the anti-anxiety medication diazepam (**10**), the HIV-1 reverse transcrip-

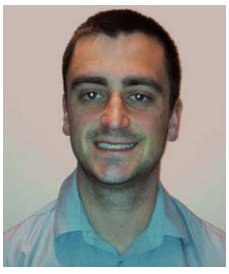


Scheme 3 Carbamazepine (**8**) and oxcarbazepine (**9**) derived from dibenzazepine (**7**)

Biographical Sketches

Tristan Reekie obtained his B.Sc. (Hons.) from the Australian National University, Canberra in 2007 where he also completed his Ph.D. in 2013 in natural product synthesis under the supervision of Prof. Martin Banwell. He then took up a postdoctoral research fellowship with Prof. Michael Kassiou at the University of Sydney in medicinal chemistry. He currently works as a postdoctoral fellow at ETH, Zurich with Prof. François Diederich.

Madeline Kavanagh completed her M.Sc. degree in July 2013 under the supervision of Prof. Michael Kassiou at the University of Sydney. She previously obtained her B.Sc. (Adv.) degree from the University of Sydney after completing an Honours year in chemistry in 2012. Her work has focused on the design and synthesis of inhibitors of the LRRK2 kinase as novel therapeutics to treat Parkinson's disease and other neurological conditions.



Mitchell Longworth completed his B.Sc. (Adv.) with Honours at the University of Sydney in 2012 under the supervision of Prof. Michael Kassiou. His honours project was based on a structure-activity relationship study of a novel oxytocin receptor agonist. He is currently working for Novartis Pharmaceuticals in the Drug Safety and Epidemiology Department.

Michael Kassiou is Professor of Medicinal Chemistry at the University of Sydney and Head of the Drug Discovery Research Unit at the Brain and Mind Research Institute. His main research interests are concerned with the understanding of drug–protein and drug-binding site interactions in order to obtain structure-activity relationships of bioactive CNS molecules, allowing the rational design of more efficacious treatments for diseases of the brain. He received his Ph.D. in chemistry from the University of New South Wales in 1992. He has been a Postdoctoral Fellow at Johns Hopkins University and a Fogarty Fellow at the National Institute of Drug Abuse, National Institutes of Health in the USA. He serves on several journal editorial boards focusing on medicinal chemistry, pharmaceutical design, and drug discovery.

tase inhibitor nevirapine (**11**), and the sedative chlordiazepoxide (**12**) (Figure 1).

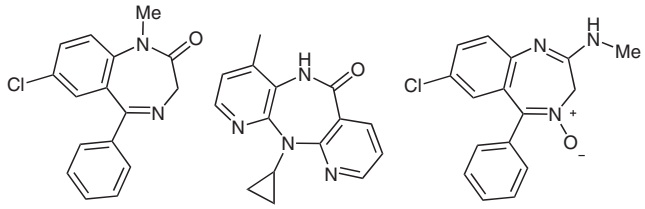
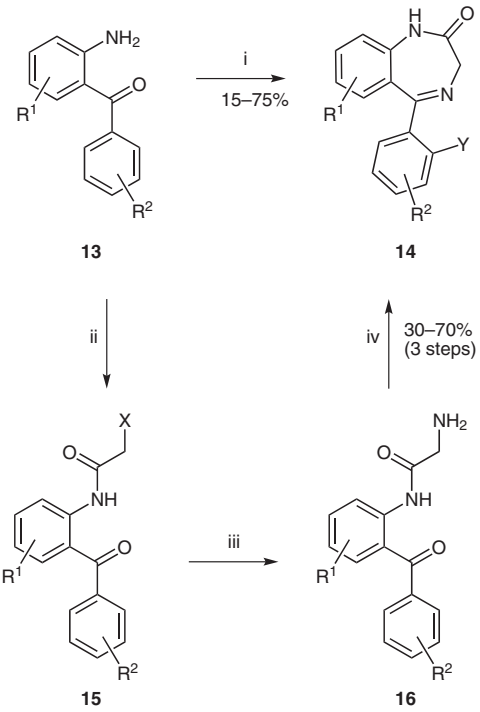


Figure 1 Biologically active 1,4-benzodiazepines diazepam (**10**), nevirapine (**11**), and chlorodiazepoxide (**12**)

A widely applicable method for the synthesis of these benzodiazepinone-type structures is shown in Scheme 4.[8] A single-step method can be employed whereby an appropriately substituted *o*-aminobenzophenone **13** reacts with a glycine ester hydrochloride (with the ethyl ester providing the best yields) to afford the target compounds **14** in 15–75% yields. Lower yields resulted when substituents were located at position Y, most likely as a result of steric hindrance. A three-step procedure has also been employed starting from the same *o*-aminobenzophenone **13** with the aniline first acylated with a haloacetyl halide to give amides **15** and subsequent aminolysis affording α-aminoamides **16**. Subsequent intramolecular Schiff base condensation afforded the benzazepines **14** in 30–70% yields from *o*-aminobenzophenone **13**.



Scheme 4 Two routes for the synthesis of variably substituted diazapinones of type **14**. *Reagents and conditions* (varied depending on substituents)*:* (i) glycine ethyl ester hydrochloride (1.5 equiv), pyridine, reflux, 15 h; (ii) α-haloacetyl halide (1.3 equiv), 3 M aq NaOH (1.3 equiv), <10 °C, 0.5 h; (iii) liquid NH_3 (excess), reflux, 5 h; (iv) toluene, reflux, 1 h.

Oxygen-Containing Seven-Membered Rings

Mono-oxygen seven-membered rings are less common in pharmaceuticals compared to nitrogen-containing analogues. Available examples are normally flanked by two aromatic moieties, as seen in the CNS active compounds doxepin (**17**), asenapine (**18**), and oxetorone (**19**) (Figure 2).

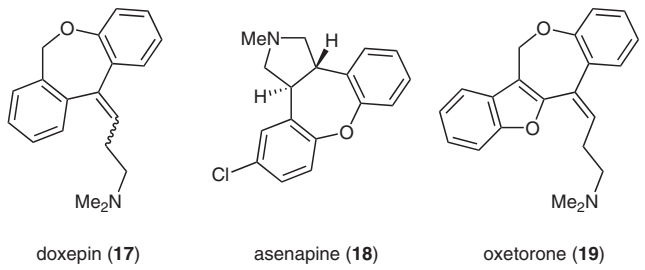
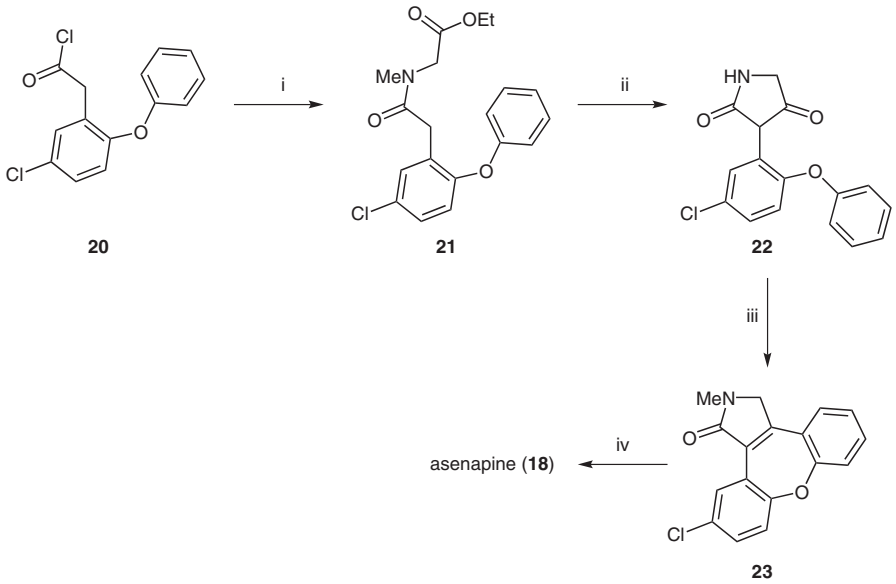


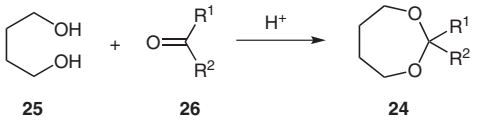
Figure 2 Biologically active benzoxapines doxepin (**17**), asenapine (**18**), and oxetorone (**19**)

The original synthesis of asenapine is illustrative of one route available to access this class of compounds commencing from precursors pre-functionalized with the biaryl ether that will form part of the oxepine ring (Scheme 5). Acid chloride **20**[9] was converted into the amide **21** via acylation with glycine ethyl ester hydrochloride followed by cyclization to form the five-membered ring and thus provide compound **22**. Cyclization promoted by H_3PO_4/P_2O_5 provides the oxepine **23** with subsequent lactam reduction affording the target asenapine (**18**). Other methods have been reported where forming the oxygen–aromatic bond is used to construct the oxepine ring.[10]

Compared to other seven-membered-ring heterocycles, dioxepines have made little impact in synthetic or medicinal chemistry and are generally used as precursors rather than final targets. Of this class, 1,3-dioxepines of type **24** have had the greatest utility, which is most likely a result of their ease of synthesis. For example, a diol of type **25** and aldehyde or ketone **26** can cyclize under acidic conditions to afford the target seven-membered ring (Scheme 6) from simple starting materials.[11]



Scheme 5 Previously reported synthesis of asenapine (**18**). *Reagents and conditions:* (i) glycine ethyl ester hydrochloride, Et_3N, DMF, r.t., time not reported; (ii) *t*-BuOK, toluene, 0 °C, 16 h; (iii) H_3PO_4/P_2O_5, 125 °C, 4 h; (iv) Na, *i*-PrOH, time and temperature not reported (yields and reagent equivalents not reported).



Scheme 6 General method for the synthesis of 1,3-dioxapines of type **24**

Sulfur-Containing Seven-Membered Rings

In a similar manner to benzoxepines and benzazapines, numerous biologically active benzothiepine-containing compounds have found success as pharmaceuticals.[12] Dosulepin (**27**) is sold as an antidepressant while the thiophene analogue bisulepin (**28**) acts as an antihistamine (Figure 3). The sulfoxide Y-23684 (**29**) is an anxiolytic and anticonvulsant that has yet to progress past animal trials, but demonstrates that the multiple oxidation states of sulfur can be utilized in drug development.[13]

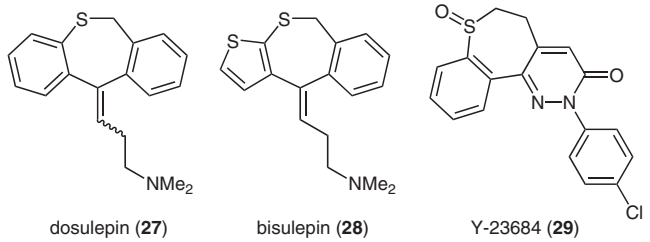
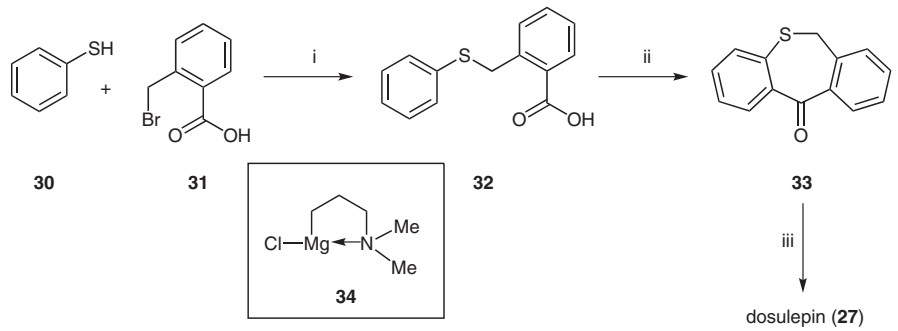


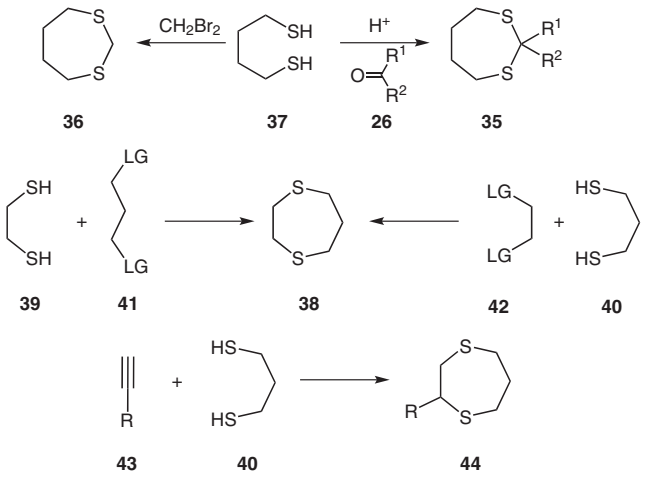
Figure 3 Biologically active benzothiepines dosulepin (**27**), bisulepin (**28**), and Y-23684 (**29**)

The greater nucleophilicity of sulfur allows for S-alkylation as a more viable method of thiepine synthesis, a challenge associated with other heteroatoms. The synthesis of dosulepin (**27**) begins with the alkylation of thiophenol (**30**) with 2-carboxybenzyl bromide (**31**) to give thioether **32** (Scheme 7).[14] Cyclization of this last compound into the thiepine **33** can be promoted by H_3PO_4/P_2O_5 and following addition of Grignard reagent **34** and dehydration, dosulepin (**27**) is obtained. Cyclization to form a more substituted thiepine is best performed under Friedel–Crafts reaction conditions from the corresponding acid chloride.[12]

Whilst dithiepines are uncommon scaffolds in medicinal chemistry, they are readily accessible by a number of synthetic routes. The synthesis of 1,3-dithiepines **35** or **36** can follow a similar path to that of the dioxepines with a dithiol **37** reacting with an appropriate aldehyde or ketone **26**, or alternatively, by reacting with an alkyl derivative such as dibromomethane (Scheme 8).[15] The improved ability to alkylate the dithiols allows for better access to the 1,4-dithiepines **38** by direct alkylation of a 1,2- or 1,3-dithioalkane **39** or **40**, respectively, with an alkane with appropriate leaving group (LG) at the 1,3- or 1,2-position **41** or **42**, respectively. 1,3-Dithianes **40** also react with alkynes **43** to form 1,4-dithiepines **44**.[16] A range of oxidative techniques have been explored to convert thioethers, including those contained in a cyclic system, into the corresponding sulfoxide or sulfone.[17]



Scheme 7 Previously reported synthesis of dosulepin (**27**). *Reagents and conditions:* (i) **31** (1.1 equiv), K_2CO_3 (2.2 equiv), acetone, reflux, 1.5 h; (ii) H_3PO_4/P_2O_5, 115 °C, 0.75 h; (iii) (a) **34** (1.5 equiv), THF, reflux, 2.5 h; (b) concd HCl (excess), 100 °C, 3 h (yields not reported).



Scheme 8 General methods for the synthesis of 1,4-dithiepines

Mixed Heteroatom Seven-Membered Rings

Seven-membered rings incorporating two different heteroatoms generally combine a nitrogen atom with either oxygen or sulfur, to give the oxazepine or thiazepine respectively. These compounds have found application in a range of areas including pharmaceuticals with the 1,3-thiazepine diltiazem (**45**) acting as a calcium channel blocker to treat hypertension and the 1,3-oxazepine amoxapine (**46**) prescribed as an antidepressant (Figure 4). The related 1,3-oxazepine CR gas or dibenzoxazepine (**47**) has been used as an incapacitating agent for riot control due to its strong lachrymatory and skin irritant effects. The synthesis of these mixed heterocycles is dependent on the heteroatoms and typically involves sequential nucleophilic aromatic substitution or alkylation/acylation reactions to afford the cyclized seven-membered ring. Seven-membered rings containing oxygen and sulfur heteroatoms are less common. Reports have primarily focused on the synthetic challenge and properties associated with this class of compounds as opposed to their applications.[15,16]

Synthesis of Oxytocin Mimetics

We have recently become interested in the synthesis of the 1,4-diazepine moiety, owing to its relevance in nonpeptidic oxytocin receptor agonists[18] **47** (WAY 267,464)[19] and **48** (Figure 5). Oxytocin has been associated with prosocial behaviour. Increased levels have been reported to improve trust, alleviate symptoms related to autism and social phobias, and reduce social anxiety.[20]

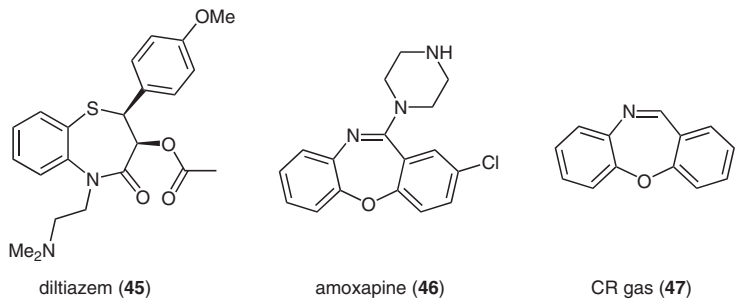


Figure 4 Biologically active benzothiazepine diltiazem (**45**) and benzoxazepines amoxapine (**46**) and CR gas (**47**)

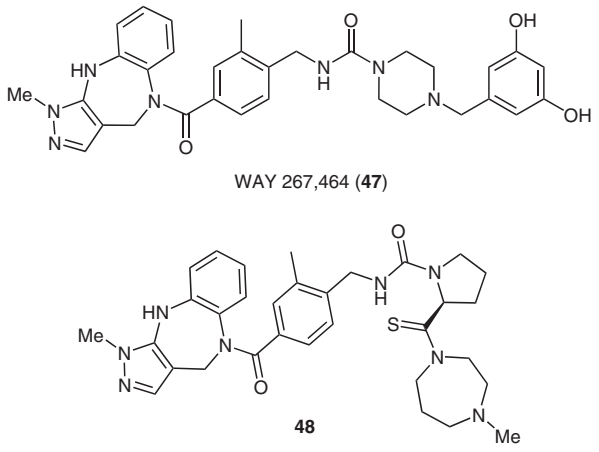
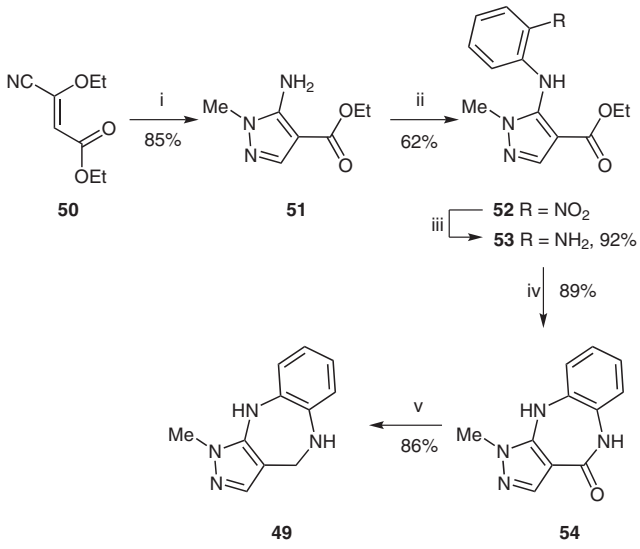


Figure 5 Nonpeptidic oxytocin receptor agonists WAY 267,464 (**47**) and compound **48**

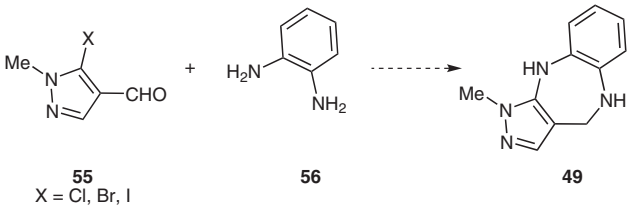
The previously reported synthesis of the benzodiazepine core **49** contained within compounds **47** and **48** is shown in Scheme 9.[21] It began with the reaction of compound **50** with *N*-methylhydrazine to give pyrazole **51** (85%), followed by a nucleophilic aromatic substitution with 1-fluoro-2-nitrobenzene to give compound **52** (62%). Reduction of the nitro moiety then gave aniline **53** (92%) that could undergo intramolecular aminolysis to give benzodiazepinone **54** (89%). Reduction of the lactam contained within this last compound gave the benzodiazepine core **49** (86%) that could be elaborated into oxytocin agonists **47** and **48**.[21]



Scheme 9 Previously reported synthesis of the diazapine core **49** of oxytocin agonists WAY 267,464 (**47**) and compound **48**. *Reagents and conditions:* (i) methylhydrazine (1.1 equiv), EtOH, reflux, 1 h; (ii) NaH (1.4 equiv), 1-fluoro-2-nitrobenzene (1 equiv), THF, 0 °C to r.t., 18 h; (iii) Pd/C (cat.), MeOH, r.t., 1 h; (iv) AcOH–*i*-PrOH (1:9), 160 °C, sealed tube, 48 h; (v) $LiAlH_4$ (14 equiv), THF, reflux, 44 h.

As part of our group's research efforts, we required access to large quantities of the nonpeptidic oxytocin receptor agonists **47** and **48**, the synthesis of which has already been reported and proceeds through compound **49**.[21,22] When repeating the syntheses of **47** and **48** on a similar reaction scale comparable yields were obtained to the work outlined in Scheme 9. However, upon necessary scale up (>10 g) the reaction sequence proved problematic with a substantial reduction in yield and challenging procedures on a large scale. Therefore, a new method of synthesis amenable to large-scale production and, if possible, tolerant towards various aromatic substituents, was required to access diazepine **49** and a library of analogues.

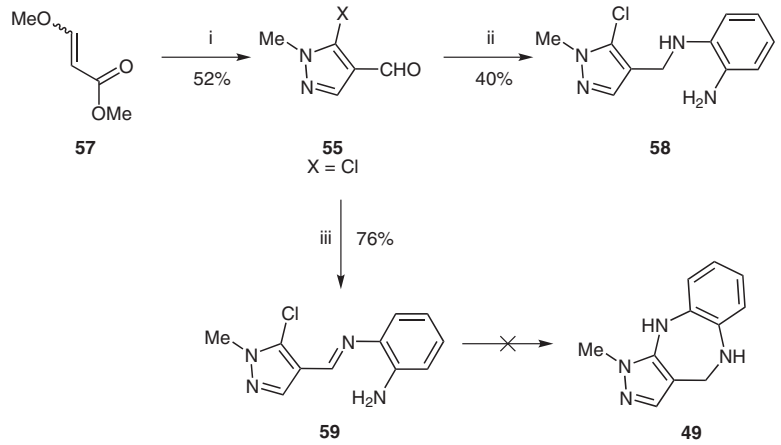
It was proposed (Scheme 10) that by inverting the nucleophilic aromatic substitution reaction so that the pyrazole unit (of type **55**) now acted as the electrophile, as opposed to in Scheme 9, with a 1,2-phenylenediamine **56** as the nucleophile, then both goals could potentially be achieved.



Scheme 10 Proposed new synthesis of diazapine **49**

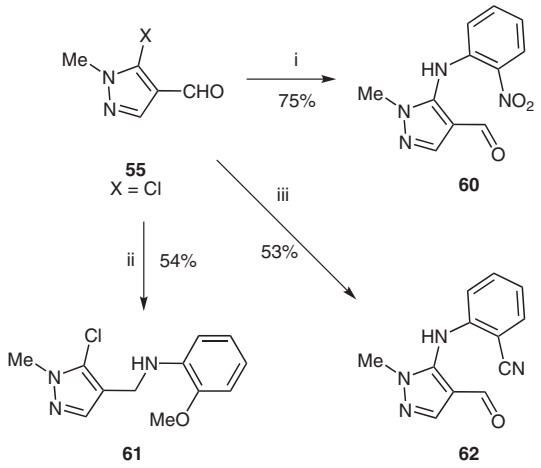
To explore the validity of this approach to diazepine **49**-like compounds we first pursued the reaction between the simplest, unsubstituted pyrazole **55** (X = Cl) and 1,2-phenylenediamine (**56**). Pyrazole **55** was synthesized from methyl 3-methoxyacrylate (**57**) and *N*-methylhydrazine followed by a Vilsmeyer–Haack formylation reaction and concomitant chlorination in 52% over two steps (Scheme 11). Pyrazole **55** and 1,2-phenylenediamine were subjected to a one-pot nucleophilic aromatic substitution in refluxing ethanol with piperidine followed by imine reduction with sodium borohydride using conditions that had been successful on related systems.[23] Unfortunately aromatic substitution did not occur under these conditions and only the product of reductive amination **58** (40%) was obtained. More forcing conditions were employed with potassium hydroxide in *N*,*N*-dimethylformamide at 120 °C[24] and without the addition of sodium borohydride, but only imine **59** was obtained. Attempts to cyclize both amine **58** and imine **59** to give diazepine **49** were unsuccessful using a variety of bases and Buchwald–Hartwig amination or Ullman reaction conditions. Changing the aryl halide electrophile to the bromo or iodo analogues of pyrazole **55** (X = Br, or I) also failed to promote the desired substitution.

Following these unsuccessful attempts it was perceived that by forcing the nucleophilic aromatic substitution to occur first, without the possibility of imine formation, that product **49**, or some suitable precursor, could be obtained. By altering the electronics of the nucleophilic aniline we hoped to improve the acidity of the nucleophilic nitrogen and destabilize the imine intermediate **59**, and thus limit its formation. 2-Nitroaniline was chosen for this purpose



Scheme 11 First generation approach to diazepine **49**. *Reagents and conditions:* (i) (a) *N*-methylhydrazine (1.1 equiv), MeOH, reflux, 16 h; (b) DMF (1.5 equiv), $POCl_3$ (3 equiv), 0 to 80 °C, 7 h; (ii) 1,2-phenylenediamine (1.1 equiv), pyridine (0.1 equiv), EtOH, reflux, 3 h, then $NaBH_4$ (2.5 equiv), 0 °C to reflux, 1 h; (iii) 1,2-phenylenediamine (3 equiv), KOH (2 equiv), DMF, 120 °C, 2 h.

as the electron-withdrawing nature of the nitro group has a significant impact on the electronics of the system while still retaining an appropriately substituted, but masked, second nitrogen atom. Thus, pyrazole **55** (X = Cl) and 2-nitroaniline were exposed to potassium hydroxide in *N*,*N*-dimethylformamide at 120 °C to give the targeted compound **60** in 75% yield (Scheme 12). Under these conditions no imine formation was observed, even following substitution, despite the excess of nitroaniline used. To validate our initial hypothesis that the electron-withdrawing nitro moiety disfavoured imine formation two different anilines were exposed to pyrazole **55** (X = Cl) under the same reaction conditions. As expected the electron-rich 2-methoxyaniline gave amine **61** following sodium borohydride reduction (54%) (attempts to isolate the imine were unsuccessful) while the electron-poor 2-aminobenzonitrile resulted in substitution to give compound **62** (53%).

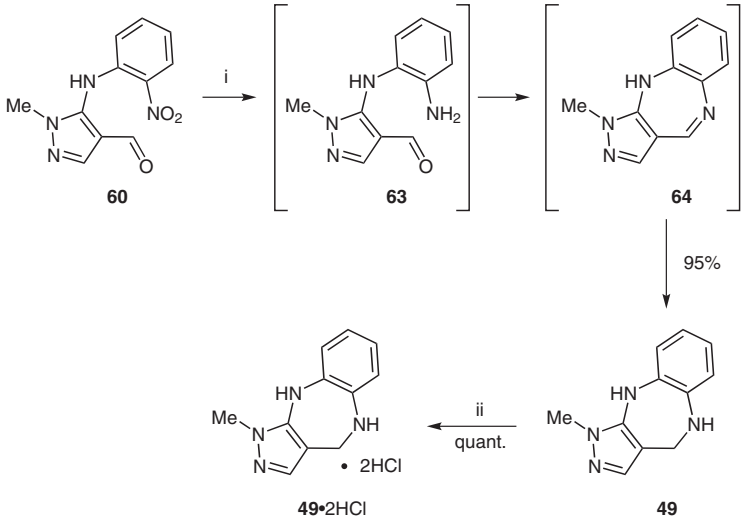


Scheme 12 Revised method for nucleophilic aromatic substitution. *Reagents and conditions:* (i) 2-nitroaniline (3 equiv), KOH (2 equiv), DMF, 120 °C, 2 h; (ii) 2-methoxyaniline (3 equiv), KOH (2 equiv), DMF, 120 °C, 2 h then $NaBH_4$ (2 equiv), MeOH, 0 °C to r.t., 0.5 h; (iii) 2-aminobenzonitrile (3 equiv), KOH (2 equiv), DMF, 120 °C, 2 h.

A range of different conditions were tested to determine the scope of this reaction. The reaction solvent was altered to ethanol, 1,4-dioxane, or THF all at refluxing temperatures to give compound **60** in 41%, 31%, or 19% yields, respectively. This showed that while the same transformation could be achieved in a number of solvents and, therefore, temperatures, *N*,*N*-dimethylformamide at 120 °C remained the most effective. Refluxing acetonitrile was unsuccessful at providing any of compound **60** with only decomposition of pyrazole **55** being observed. Changing the base from potassium hydroxide to triethylamine, *N*,*N*-diisopropylethylamine (DIPEA), or potassium carbonate did not result in any reaction when carried out in *N*,*N*-dimethylformamide at 120 °C, while sodium ethoxide gave compound **60** in a lower 52% yield.

With compound **60** in hand we proceeded with the rest of our proposed synthetic route. Exposure of **60** to palladium on carbon in methanol under an atmosphere of hydrogen effected reduction of the aromatic nitro moiety and cyclization to give target diazepine **49** in 95% yield (Scheme 13). The mechanism likely follows initial reduction of the nitro moiety to the corresponding aniline **63**, which can then undergo an intramolecular Schiff base condensation to give imine **64**. Under the reducing conditions employed, the imine was then reduced to give the target diazepine **49**. The hydrogenation catalyst appeared to be unimportant for this transformation with Pd/Al_2O_3, Pt/C, and Raney Ni all effecting the same transformation in >90% yield. A Zn/HCl reductive system was also successful in providing diazepine **49**, but in a reduced yield of 70%.

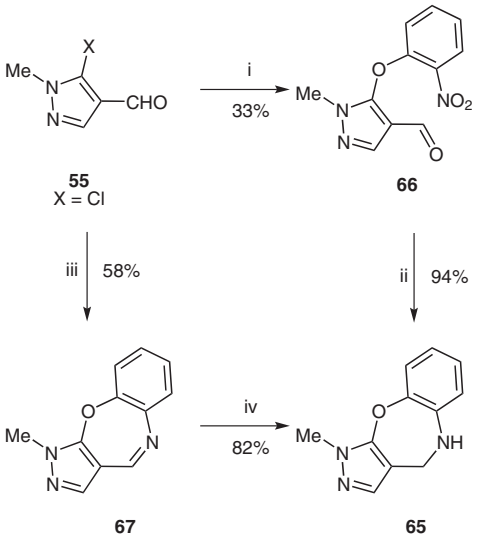
With a new route to the target diazepine **49** obtained, the procedure was repeated to determine if these methods would be amenable to large scale (0.1 mol) production. While some reduction in yield was observed (62% and 91% cf. 75% and 95% respectively) in scale up, large quantities of diazepine **49** could be obtained quickly and



Scheme 13 Tandem reductive cyclization to form diazepine **49**. *Reagents and conditions:* (i) Pd/C (cat.), H_2 (1 atm), MeOH, r.t., 16 h; (ii) 4.0 M HCl in 1,4-dioxane (2 equiv), THF, r.t., 2 min.

easily for quantitative conversion to the crystalline hydrochloride salt **49**·2HCl.

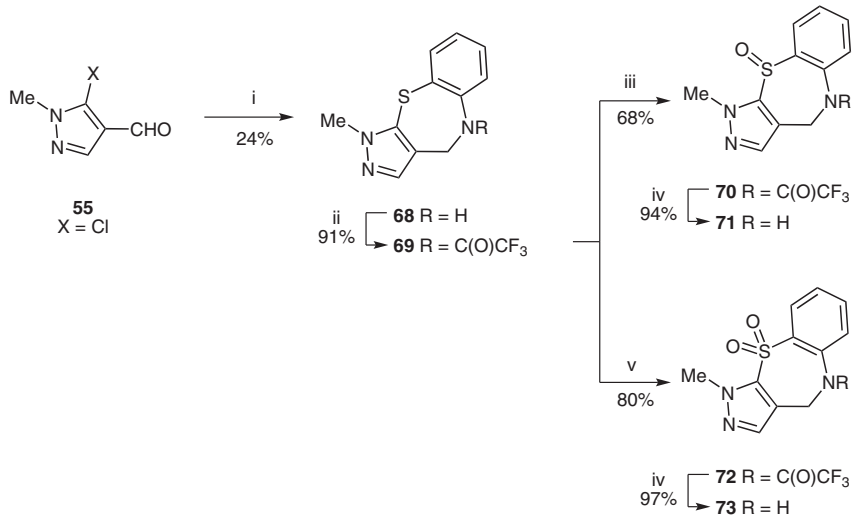
The applicability of this method to the synthesis of analogues of diazepine **49** was then explored with focus on varying the heteroatoms contained within the seven-membered ring. Towards the synthesis of oxazepine **65**, 2-nitrophenol was subjected to the same reaction conditions with pyrazole **55** (X = Cl), but no reaction took place. Changing from conventional heating to microwave irradiation promoted the desired transformation to give compound **66** albeit in a reduced 33% yield (Scheme 14). Subjecting **66** to tandem reductive cyclization conditions gave the target oxazepine **65** in 94% yield. When 2-aminophenol was exposed to the same reaction conditions initially trialed for nitrogen analogue **56**, in contrast to that result (Scheme 11) the desired nucleophilic aromatic substitution took place along with concomitant Schiff base condensation to give imine **67** (58%). While the order of reaction was most likely nucleophilic aromatic substitution followed by intramolecular Schiff base condensation, no intermediates were isolated to support or disprove this proposal. Reduction of the imine contained within compound **67** with sodium borohydride gave oxazepine **65** in 82% yield, which was identical, in all respects, to that obtained via the nitro derivative.



Scheme 14 Synthesis of oxazepine analogue **65**. *Reagents and conditions:* (i) 2-nitrophenol (3 equiv), KOH (2 equiv), DMF, microwave, 120 °C, 0.5 h; (ii) Pd/C (cat.), H_2 (1 atm), MeOH, r.t., 18 h; (iii) 2-aminophenol (3 equiv), KOH (2 equiv), DMF, 120 °C, 2 h; (iv) $NaBH_4$ (2 equiv), MeOH, 0 °C to r.t., 1.5 h.

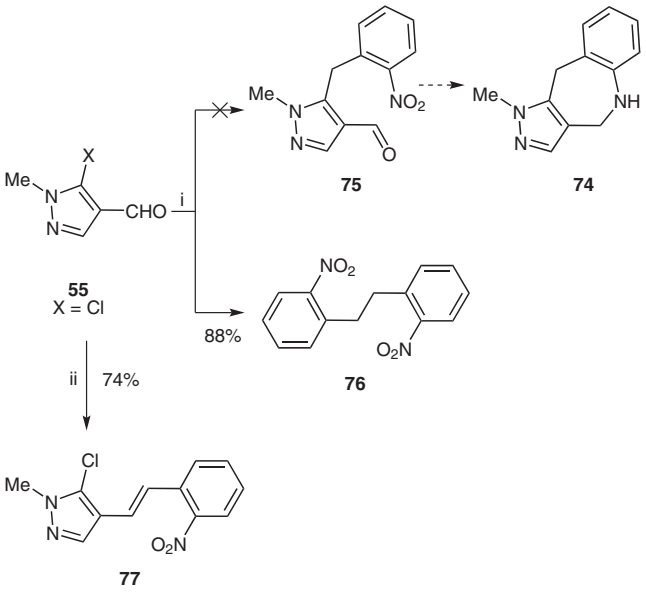
Following on from these results, a route to the thiazepine **68** was also investigated. Due to the greater nucleophilicity of sulfur a one-pot method was utilized whereby pyrazole **55** (X = Cl) was combined with 2-aminothiophenol and piperidine in refluxing ethanol and then treated with sodium borohydride to afford the thiazepine **68** in 24% yield (Scheme 15). The ability to alter the oxidation state of the sulfur atom contained within thiazepine **68** was also investigated as a way to provide a greater range of potentially interesting analogues of the heterocyclic unit. To achieve this goal the azepine nitrogen was first protected as the trifluoroacetamide **69** (91%). Partial oxidation of the thioether **69** was achieved with one equivalent of hydrogen peroxide in acetic acid[25] to afford the sulfoxide **70** in 68% yield (87% based on recovered starting material). Nitrogen deprotection with potassium carbonate in methanol gave the racemic thiazepine **71** in 94% yield. Complete oxidation of the thioether **69** to the sulfone **72** could be achieved with excess hydrogen peroxide in acetic acid (80%) and subsequent nitrogen deprotection afforded compound **73** (97%).

The final target to be investigated within this series was the corresponding azepine **74**, which was thought to be obtained from the initial reaction between pyrazole **55** (X = Cl) and 2-nitrotoluene to give compound **75**



Scheme 15 Synthesis of thiazepine analogue **68** and subsequent oxidation of the thioether to give sulfoxide **71** and sulfone **73**. *Reagents and conditions:* (i) 2-aminothiophenol (1.1 equiv), piperidine, EtOH, reflux, 3 h, then $NaBH_4$ (2.5 equiv), 0 °C to reflux, 1 h; (ii) TFAA (1.5 equiv), Et_3N (3.0 equiv), THF, 0 °C 3 h, r.t., 18 h; (iii) 30% aq H_2O_2 (1 equiv), AcOH, 80 °C, 2 h; (iv) K_2CO_3 (3 equiv), MeOH, r.t., 18 h; (v) 30% aq H_2O_2 (3 equiv), AcOH, 80 °C, 4 h.

(Scheme 16). Unfortunately, under the previously defined conditions (KOH, DMF, 120 °C), the starting pyrazole **55** was returned unreacted and compound **76**, resulting from a dimerization of 2-nitrotoluene, was also isolated (88%).[26] The use of different bases (KO*t*-Bu or *n*-BuLi) did not give any of the desired product **75**. When the reaction with potassium hydroxide in *N*,*N*-dimethylformamide was performed at room temperature for 18 hours then a condensation reaction took place to yield compound **77** (74%). ^{1}H NMR spectroscopy showed the two olefinic protons as doublets at δ = 6.75 and 7.35 with the coupling constant (J = 16.3 Hz) indicating a *E*-double bond. Work towards the synthesis of azepine **74** is still ongoing, but to date this compound has remained elusive.



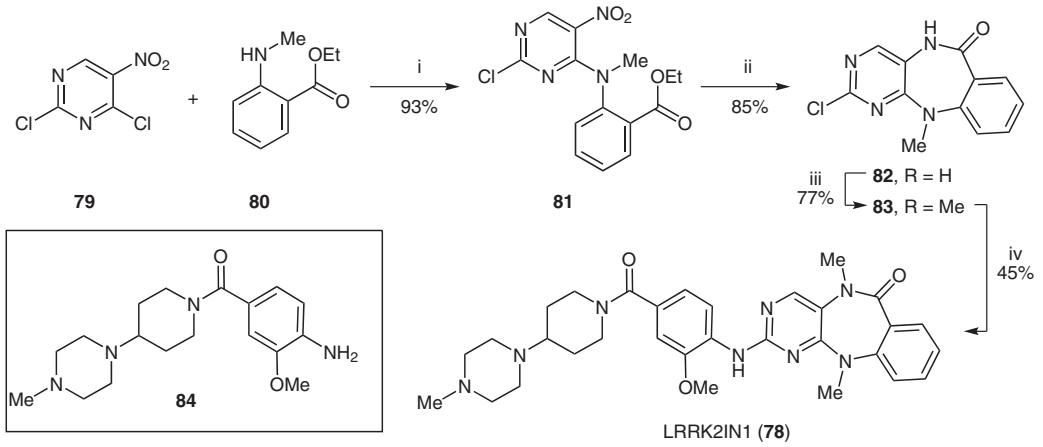
Scheme 16 Attempts to synthesize azepine **74**. *Regents and conditions:* (i) 2-nitrotoluene (3 equiv), KOH (2 equiv), DMF, 120 °C, 2 h; (ii) 2-nitrotoluene (3 equiv), KOH (2 equiv), DMF, r.t., 18 h.

Synthesis of Leucine-Rich Repeat Kinase 2 (LRRK2) Inhibitors

Mutations within the PARK8 gene have been implicated in the increased risk of developing Parkinson's disease in humans.[27] Mutant leucine-rich repeat kinase 2 (LRRK2) isoforms commonly exhibit elevated kinase activity and consequently compounds that inhibit LRRK2 have been sought as potential therapeutic treatments for Parkinson's disease.[28] LRRK2IN1 (**78**), incorporating a pyrimidobenzodiazepinone moiety, was identified as a potent inhibitor of the LRRK2 by high throughput screening.[29] The previously reported synthesis of LRRK2IN1 (**78**) (Scheme 17) began with a nucleophilic aromatic substitution between the pyrimidine **79** and aniline **80** to give compound **81** in 93% yield.[29] Reduction of the aromatic nitro moiety was accompanied by intramolecular aminolysis to form the diazepinone **82** (85%) that could then be methylated to give **83** (77%). A Buchwald–Hartwig amination between the last compound and aniline **84** afforded the target LRRK2 inhibitor LRRK2IN1 (**78**) in 45% yield.

While LRRK2N1 has been shown to be a potent inhibitor of LRRK2 in vitro and in peripheral tissues in vivo it is not biologically available in the brain. Using computer modeling, our group predicted that metabolism and a poor pharmacokinetic profile may be preventing LRRK2IN1 from crossing the blood-brain barrier.

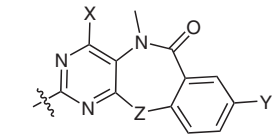
Attempts have been made within the group to synthesize analogues that retain the potency of LRRK2IN1 but possess more favourable pharmacokinetics by making minor



Scheme 17 Previously reported synthesis of the LRRK2 inhibitor LRRK2IN1 (**78**). *Reagents and conditions:* (i) **25** (1.5 equiv), DIPEA (2 equiv), 1,4-dioxane, 50 °C, 6 h; (ii) Fe(0) powder (10 equiv), AcOH, 50 °C, 9 h; (iii) MeI (1.5 equiv), NaH (3.1 equiv), DMA, –10 to 0 °C, no time reported; (iv) 30 (1 equiv), $Pd_2(dba)_3$ (cat.), X-Phos (cat.), K_2CO_3 (equiv), *t*-BuOH, 100 °C, 4 h.

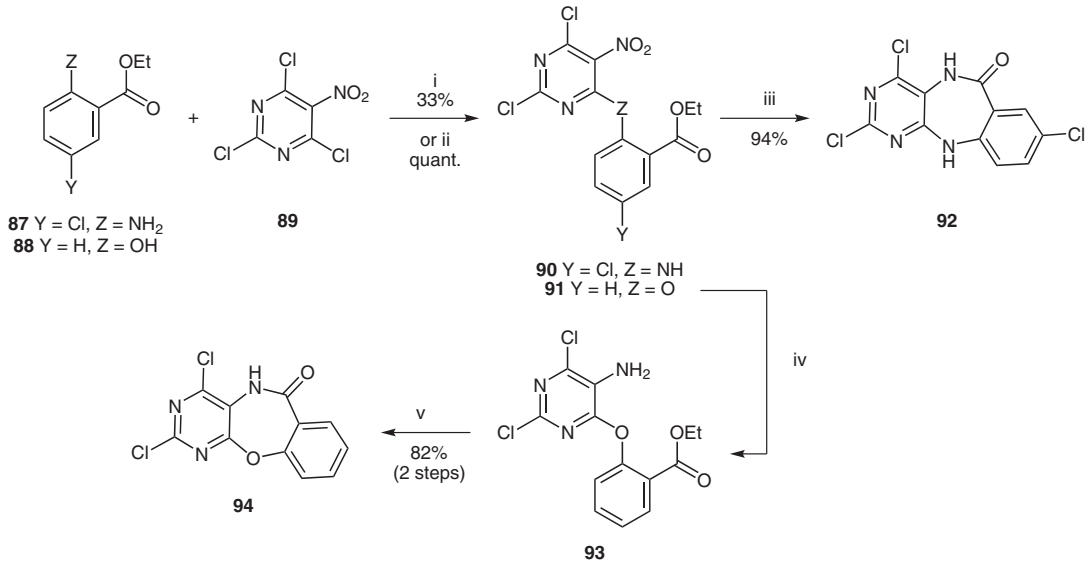
modifications to the pyrimido-benzodiazepinone core (Figure 6). Diazepinone **85** and oxazepinone **86** were selected as our initial synthetic targets through which we foresaw to access the reduced azepine derivatives through carbonyl reduction.

Our initial synthetic route mimicked that described previously for lead compound LRRK2IN1 (Scheme 17). Aniline **87** or phenol **88** were reacted with 2,4,6-trichloro-5-nitropyrimidine (**89**) to give the corresponding compound **90** or **91** in 33% or quantitative yield, respectively (Scheme 18). Along with the isolation of compound **90** a second compound arising from disubstitution, whereby the aniline also substituted for the chloride at the 2-position, was isolated in 22% yield despite an excess of the pyrimidine.



LRRK2IN1 (**78**) X, Y = H, Z = NMe
85 X, Y = Cl, Z = NMe
86 X = Cl, Y = H, Z = O

Figure 6 LRRK2IN1 and potentially metabolically stable analogues **85** and **86**



Scheme 18 The synthesis of LRRK2IN1 azepinone analogues **92** and **94**. *Reagents and conditions:* (i) **87** (0.66 equiv), DIPEA (1.3 equiv), 1,4-dioxane, 55 °C, 3 h; (ii) **88** (0.66 equiv), DIPEA (1.3 equiv), 1,4-dioxane, r.t., 4 h; (iii) Fe powder (10 equiv), AcOH, 130 °C (sealed tube), 20 h; (iv) Fe powder (10 equiv), AcOH, 60 °C, 18 h: (v) Me_3Al (1.6 equiv), CH_2Cl_2, 0 °C, 1 h, reflux, 18 h.

Attempts to reduce the aromatic nitro moiety and cyclize were somewhat more problematic than that experienced in the parent system (**81** to **82**, Scheme 17).[29] For the aniline derivative **90**, higher temperatures (130 °C cf. 50 °C) and sealed tube conditions were required to afford diazepinone **92** (94%) though this transformation could still be achieved in a single-pot procedure. The oxygen analogue **91** was accessed through a two-step procedure whereby the nitro moiety was first reduced to the corresponding aniline **93** and then treated with trimethylaluminum to effect cyclization to give oxazepinone **94** (82% over 2 steps).

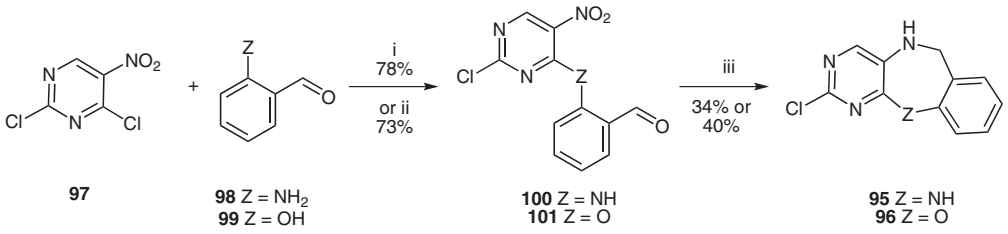
Unfortunately, attempts to reduce the carbonyl associated with compounds **92** and **94** to afford the corresponding diazepine **95** or oxazepine **96** were unsuccessful using a range of standard reducing conditions including lithium aluminum hydride or borane–tetrahydrofuran complex. The halogen substituents decorating these scaffolds as metabolic blocking groups or handles for further functionalization via Buchwald–Hartwig chemistry prevented further reductive conditions from being attempted. Therefore, in an attempt to access the reduced systems, our success with diazepine **49**, described above, led us to develop a similar synthetic route (Scheme 19). Thus, the dichloropyridimine **97** was reacted with 2-aminobenzaldehyde (**98**) or 2-hydroxybenzaldehyde (**99**) to afford compounds **100** and **101**, respectively. The presence of the chlorides proved somewhat problematic for the reductive cyclization step with their propensity to be cleaved in the reaction. Consequently, reductive systems such as palladium on carbon were avoided. Mild reduction using a Zn/H^+ system was unsuccessful, as was initial reduction to the corresponding aniline (with Fe/H^+) and attempts at intramolecular reductive animation. Finally, a successful one-pot reduction of the nitro moiety and concomitant reductive cyclization was achieved using catalytic platinum(IV) oxide under an atmosphere of hydrogen in refluxing methanol without cleavage of the aromatic chlorides. Thus, compounds **95** and **96** were obtained from precursors **100** and **101** in 34% and 40% yields, respectively, and thereby provided the diazepine and oxazepine analogues of the parent compound **78**. The synthesis of these derivatives further validated the versatility of the synthetic route we have developed to access various heteroaromatic substituted seven-membered heterocycles.

Conclusion

Seven-membered-ring heterocycles are a key motif in numerous commercially significant compounds across a range of industries and in particular in pharmaceuticals. Their methods of synthesis are widely variable depending on the heteroatom(s) and substitution patterns required. We have provided a brief review of some of the key compounds in this area as well as methods for their synthesis. These procedures have been adapted to provide new methods for the synthesis of key compounds to target the oxytocin receptor and inhibit LRRK2, both of which have been implicated in important neurological disorders.

All reactions were performed under an atmosphere of N_2 or argon unless otherwise specified. THF, toluene, and 1,4-dioxane were dried over Na wire and distilled from, in the case of THF, sodium benzophenone ketyl. CH_2Cl_2, MeOH, EtOH, and MeCN were distilled from CaH_2. AR Grade acetone was used as purchased. Commercially available chemicals were used as purchased. Analytical TLC was performed using Merck aluminum-backed silica gel 60 F254 (0.2 mm) plates which were visualized using shortwave (254 nm) and/or longwave (365 nm) UV fluorescence. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) silica gel. Melting points were measured in open capillaries using a Stuart SMP10 melting point apparatus and are uncorrected. Infrared absorption spectra were recorded on a Bruker Alpha FT-IR spectrophotometer. Nuclear magnetic resonance spectra were recorded at 300 K using a Bruker Avance 200 NMR (300.1 MHz) spectrometer relative to the residual protonated solvent resonance. Assignment of signals was assisted by COSY, DEPT, HSQC, and HMBC experiments where necessary. LRMS were recorded using electrospray ionization (ESI) or atmospheric-pressure chemical ionization (APCI) recorded on a Finnigan LCQ ion trap spectrometer.

5-Chloro-1-methyl-1*H*-pyrazole-4-carbaldehyde (55, X = Cl)
A magnetically stirred solution of methyl 3-methoxyacrylate (20.0 g, 172.2 mmol) in MeOH (100 mL) was treated slowly with *N*-methylhydrazine (10.0 mL, 189.4 mmol) and then heated at reflux for 16 h. The resulting mixture was cooled to r.t. then concentrated under reduced pressure to afford an orange solid that was dissolved in DMF (19.9 mL, 258.4 mmol) and cooled to 0 °C. The resulting mixture was treated slowly with $POCl_3$ (48.1 mL, 516.6 mmol) and then heated at 80 °C for 7 h. It was cooled and poured slowly into ice-cold 20% aq Na_2CO_3 soln (600 mL). The aqueous solution was then extracted with $CHCl_3$ (5 × 100 mL); the combined organic phases were washed with brine (1 × 100 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford an orange solid. Recrystallization (CH_2Cl_2–hexane) afforded **55** (X = Cl, 12.87 g, 52%) as yellow crystals, mp 77–78 °C; R_f = 0.44 (EtOAc–hexane, 1:1).



97
98 Z = NH_2
99 Z = OH
100 Z = NH
101 Z = O
95 Z = NH
96 Z = O

Scheme 19 The synthesis of diazapine **95** and oxazepine **96**. *Reagents and conditions:* (i) **98** (0.66 equiv), DIPEA (1.3 equiv), 1,4-dioxane, 55 °C, 2 h; (ii) **99** (0.66 equiv), DIPEA (1.3 equiv), 1,4-dioxane, 50 °C, 1.6 h, r.t., 3 h; (iii) PtO_2 (cat.), H_2 (1 atm), MeOH, reflux, 18 h.

IR (ZnSe cell, film): 1683, 1529, 1424, 1390, 1196, 814, 770 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.82 (s, 1 H), 7.95 (s, 1 H), 3.89 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.5 (CH), 140.1 (CH), 132.5 (C), 119.1 (C), 36.2 (CH_3).

LRMS (ESI+): *m*/*z* (%) = 145 ([M + H]$^+$, 100).

2-{[(5-Chloro-1-methyl-1*H*-pyrazol-4-yl)methyl]amino}aniline (58)

A magnetically stirred solution of **55** (X = Cl, 150 mg, 1.04 mmol), 1,2-phenylenediamine (124 mg, 1.14 mmol), and piperidine (11 μL, 0.1 mmol) in EtOH (5 mL) was heated at reflux for 3 h (TLC monitoring, no starting aldehyde **55** remained). The mixture was cooled to 0 °C and treated, in portions, with $NaBH_4$ (98 mg, 2.6 mmol) and once all was dissolved, the mixture was heated to reflux for 1 h then evaporated to afford a yellow residue. The residue was dissolved in sat. $NaHCO_3$ soln (15 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a brown oil that solidified upon standing. The residue was subjected to flash column chromatography (silica gel, EtOAc–hexane, 3:7, gradient elution) and the relevant fractions were concentrated [R_f = 0.65 (EtOAc–hexane, 1:1)] to afford **58** (98 mg, 40%) as a light brown solid; mp 92–95 °C.

IR (ZnSe cell, film): 3381, 3277, 3045, 2961, 1594, 1508, 1457, 1275 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.51 (s, 1 H), 6.59–6.73 (m, 4 H), 4.13 (s, 2 H), 3.81 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 139.9 (CH), 138.1 (C), 137.8 (C), 127.3 (C), 120.9 (CH), 120.0 (CH), 117.8 (C), 117.4 (CH), 113.5 (CH), 39.0 (CH_3), 36.4 (CH_2).

LRMS (ESI+): *m*/*z* (%) = 237/239 ([M + H]$^+$, 100/37).

(*E*)-2-{[(5-Chloro-1-methyl-1*H*-pyrazol-4-yl)methylene]amino}aniline (59)

A magnetically stirred solution of pyrazole **55** (X = Cl, 500 mg, 3.46 mmol) and 1,2-phenylenediamine (1.12 g, 10.38 mmol) in DMF (4 mL) was treated with powdered KOH (388 mg, 6.92 mmol) and then heated at 120 °C for 2 h. The resulting mixture was cooled to r.t. then treated with sat. aq NH_4Cl (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (1 × 10 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The oil was subjected to flash column chromatography (silica gel, EtOAc–hexane, 1:4 → 1:1 gradient elution) and the relevant fractions were concentrated [R_f = 0.44 (EtOAc–hexane, 1:1)] to afford **59** (617 mg, 76%) as a yellow solid; mp 88–89 °C.

IR (ZnSe cell, film): 3319, 1625, 1603, 1543, 1491, 1458, 1413, 1397, 1330, 1283, 1268, 1250, 1188, 990 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.28 (s, 1 H), 7.93 (s, 1 H), 6.94 (m, 2 H), 6.65 (m, 2 H), 4.22 (br s, 2 H), 3.79 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.6 (CH), 142.1 (C), 138.7 (CH), 137.4 (C), 129.3 (C), 127.5 (CH), 118.4 (CH), 117.6 (C), 116.9 (CH), 115.4 (CH), 36.3 (CH_3).

LRMS (ESI+): *m*/*z* (%) = 235 ([M + H]$^+$, 100).

HRMS (ESI+): *m*/*z* [M – H$^•$]$^+$ calcd for $C_{11}H_{10}{}^{35}ClN_4$: 233.0594; found: 233.0589.

1-Methyl-5-[(2-nitrophenyl)amino]-1*H*-pyrazole-4-carbaldehyde (60)

A magnetically stirred solution of pyrazole **55** (X = Cl, 5.78 g, 40.0 mmol) and 2-nitroaniline (16.56 g, 120.0 mmol) in DMF (40 mL) was treated with powdered KOH (4.49 g, 80.0 mmol) and then heated at 120 °C for 2 h. The resulting mixture was cooled to r.t. then treated with sat. aq NH_4Cl (500 mL) and extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with brine (1 × 100 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. This oil was subjected to flash column chromatography (silica gel, EtOAc–hexane, 1:4 → 1:1 gradient elution) and the relevant fractions were concentrated [R_f = 0.33 (EtOAc–hexane, 1:1)] to afford **60** (7.38 g, 75%) as a yellow, crystalline solid; mp 102–105 °C.

IR (ZnSe cell, film): 3340, 1679, 1613, 1579, 1506, 1338, 1271, 1226, 1149, 742 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.74 (s, 1 H), 9.35 (s, 1 H), 8.22 (d, *J* = 8.4 Hz, 1 H), 7.97 (s, 1 H), 7.46 (t, *J* = 8.1 Hz, 1 H), 6.98 (t, *J* = 8.1 Hz, 1 H), 6.60 (d, *J* = 8.4 Hz, 1 H), 3.72 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.2 (CH), 140.9 (CH), 140.3 (C), 140.1 (C), 136.1 (CH), 134.6 (C), 126.6 (CH), 120.2 (CH), 116.2 (C, CH, 2 overlapping signals), 35.8 (CH_3).

LRMS (ESI+): *m*/*z* (%) = 269 ([M + Na]$^+$, 100).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{10}N_4NaO_3$: 269.0651; found: 269.0646.

***N*-[(5-Chloro-1-methyl-1*H*-pyrazol-4-yl)methyl]-2-methoxyaniline (61)**

A magnetically stirred solution of pyrazole **55** (X = Cl, 500 mg, 3.46 mmol) and 2-methoxyaniline (1.12 g, 10.38 mmol) in DMF (4 mL) was treated with powdered KOH (388 mg, 6.92 mmol) and then heated at 120 °C for 2 h. The resulting mixture was cooled to 0 °C and MeOH (30 mL) was added followed by $NaBH_4$ (262 mg, 6.92). The resulting solution was warmed to r.t. and stirred for a further 0.5 h then treated with sat. aq NH_4Cl (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (1 × 10 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The oil was subjected to flash column chromatography (silica gel, EtOAc–hexane, 1:4 → 1:1 gradient elution) and the relevant fractions were concentrated [R_f = 0.42 (EtOAc–hexane, 1:1)] to afford **61** (470 mg, 54%) as a yellow oil.

IR (ZnSe cell, film): 3200, 1601, 1509, 1454, 1428, 1413, 1396, 1341, 1301, 1288, 1244, 1220, 1177, 1125, 1049, 1026, 990, 847, 796, 735, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.41 (s, 1 H), 6.78 (dt, *J* = 1.5, 7.5 Hz, 1 H), 6.67 (d, *J* = 7.5 Hz, 1 H), 6.69 (m, 2 H), 4.27 (br s, 1 H), 4.05 (s, 2 H), 3.72 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.0 (C), 138.8 (CH), 137.8 (C), 125.9 (C), 121.3 (CH), 117.0 (CH), 115.9 (C), 110.2 (CH), 109.5 (CH), 55.4 (CH_3), 37.8 (CH_2), 36.4 (CH_3).

LRMS (ESI+): *m*/*z* (%) = 252 ([M + H]$^+$, 100).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{14}{}^{35}ClN_3NaO$: 274.0723; found: 274.0717.

2-[(4-Formyl-1-methyl-1*H*-pyrazol-5-yl)amino]benzonitrile (62)

A magnetically stirred solution of pyrazole **55** (X = Cl, 500 mg, 3.46 mmol) and 2-aminobenzonitrile (1.22 g, 10.38 mmol) in DMF (4 mL) was treated with powdered KOH (388 mg, 6.92 mmol) and then heated at 120 °C for 2 h. The resulting mixture was cooled to r.t. then treated with sat. aq NH_4Cl (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (1 × 10 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The residue was subjected to flash column chromatography (silica gel, EtOAc–hexane, 1:4 → 1:1 gradient elution) and the relevant fractions were concentrated [R_f = 0.41 (EtOAc–hexane, 1:1)] to afford **62** (415 mg, 53%) as a yellow oil.

IR (ZnSe cell, film): 2222, 1672, 1636, 1602, 1582, 1559, 1542, 1517, 1506, 1497, 1454, 1395, 1290, 1191, 839, 830, 759 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.65 (s, 1 H), 7.80 (s, 1 H), 7.58 (s, 1 H), 7.49 (d, *J* = 7.5 Hz, 1 H), 7.38 (t, *J* = 8.0 Hz, 1 H), 6.97 (t, *J* = 7.5 Hz, 1 H), 6.55 (d, *J* = 8.0 Hz, 1 H), 3.51 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.2 (CH), 145.2 (C), 142.7 (C), 140.9 (CH), 134.3 (CH), 133.5 (CH), 122.3 (CH), 116.8 (CH), 116.6 (C), 114.4 (C), 101.5 (C), 36.3 (CH_3).

LRMS (ESI+): *m*/*z* (%) = 227 ([M + H]$^+$, 100).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{11}N_4O$: 227.0933; found: 227.0927.

1-Methyl-1,4,5,10-tetrahydrobenzo[*b*]pyrazolo[3,4-*e*][1,4]diazepine (49)

A suspension of pyrazole **60** (3.94 g, 16.0 mmol) and 10% Pd/C (200 mg) in MeOH (160 mL) was stirred magnetically at r.t. under an atmosphere of H_2 (1 atm) for 16 h. The resulting mixture was filtered through Celite and the solids thus retained were washed with MeOH (3 × 20 mL). The combined filtrates were concentrated under reduced pressure to afford a yellow powder. Recrystallization (CH_2Cl_2–hexane) afforded **49** (3.04 g, 95%) as a white powder; mp 205–207 °C; R_f = 0.43 (MeOH–CH_2Cl_2, 1:9).

IR (ZnSe cell, film): 3293, 1560, 1505, 1393, 1318, 761 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.99 (s, 1 H), 7.05 (d, *J* = 7.6 Hz, 1 H), 6.97 (s, 1 H), 6.81 (d, *J* = 7.6 Hz, 1 H), 6.73 (t, *J* = 7.6 Hz, 1 H), 6.64 (t, *J* = 7.6 Hz, 1 H), 5.36 (s, 1 H), 3.86 (s, 2 H), 3.67 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 140.9 (C), 139.5 (C), 135.0 (CH), 133.0 (C), 121.7 (CH), 120.8 (CH), 120.2 (CH), 118.9 (CH), 101.5 (C), 43.4 (CH_2), 35.0 (CH_3).

LRMS (ESI+): *m*/*z* (%) = 201 ([M + H]$^+$, 100).

1-Methyl-1,4,5,10-tetrahydrobenzo[*b*]pyrazolo[3,4-*e*][1,4]diazepine Dihydrochloride (49·2HCl)

A magnetically stirred solution of diazepine **49** (3.47 g, 17.33 mmol) in THF (57 mL) was treated with 4.0 M HCl in 1,4-dioxane (8.6 mL, 34.6 mmol) and a white precipitate formed immediately. The precipitate was collected and dried under reduced pressure to afford **49**·2HCl (4.1 g, quant.) as a white solid; mp >227 °C (dec.).

IR (ZnSe cell, film): 3521, 2451, 1632, 1584, 1547, 1505, 1438, 1366, 1212, 1089, 885 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.51 (s, 1 H), 7.71 (d, *J* = 7.5 Hz, 1 H), 7.59 (d, *J* = 8.1 Hz, 1 H), 7.46 (s, 1 H), 7.63 (t, *J* = 7.6 Hz, 1 H), 7.02 (t, *J* = 7.6 Hz, 1 H), 4.36 (s, 2 H), 3.86 (s, 3 H); NH signal not observed.

^{13}C NMR (75 MHz, DMSO-d_6): δ = 140.1 (C), 135.9 (C), 135.7 (CH), 129.4 (C), 125.8 (CH), 125.0 (CH), 121.3 (CH), 121.0 (CH), 96.9 (C), 45.6 (CH_2), 35.6 (CH_3).

LRMS (ESI+): *m*/*z* (%) = 201 ([M + H]$^+$, 100).

Anal. Calcd for $C_{11}H_{13}N_4$·2HCl: C, 48.37; H, 5.17; N, 20.51. Found: C, 48.37; H, 5.13; N, 20.45.

1-Methyl-5-(2-nitrophenoxy)-1*H*-pyrazole-4-carbaldehyde (66)

A solution of pyrazole **55** (X = Cl, 500 mg, 3.46 mmol), 2-nitrophenol (1.44 g, 10.38 mmol), and powdered KOH (388 mg, 6.92 mmol) in DMF (4 mL) was irradiated in a CEM Explorer™ microwave reactor at 120 °C for 0.5 h. The resulting mixture was cooled to r.t. then treated with sat. aq NH_4Cl (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (1 × 10 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The oil was subjected to flash column chromatography (silica gel, EtOAc–hexane, 1:4 → 1:1 gradient elution) and the relevant fractions were concentrated [R_f = 0.26 (EtOAc–hexane, 1:1)] to afford **66** (282 mg, 33%) as a yellow solid; mp 88–89 °C.

IR (ZnSe cell, film): 1737, 1680, 1526, 1442, 1350, 1232, 874, 824, 760 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.44 (s, 1 H), 8.05 (d, *J* = 8.1 Hz, 1 H), 7.90 (s, 1 H), 7.58 (t, *J* = 7.9 Hz, 1 H), 7.34 (t, *J* = 7.9 Hz, 1 H), 7.03 (d, *J* = 8.1 Hz, 1 H), 3.82 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.4 (CH), 149.7 (C), 148.8 (C), 140.5 (CH), 139.9 (C), 134.7 (CH), 126.3 (CH), 125.2 (CH), 118.4 (CH), 109.8 (C), 34.8 (CH_3).

LRMS (ESI+): *m*/*z* (%) = 248 ([M + H]$^+$, 100).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{10}N_3O_4$: 248. 0671; found: 248.0666.

1-Methyl-4,5-dihydro-1*H*-benzo[*b*]pyrazolo[4,3-*f*][1,4]oxazepine (65)

Method A: A suspension of pyrazole **66** (300 mg, 1.21 mmol) and 10% Pd/C (20 mg) in MeOH (15 mL) was stirred magnetically at r.t. under an atmosphere of H_2 (1 atm) for 18 h. The resulting mixture was filtered through Celite and the solids thus retained were washed with MeOH (3 × 20 mL). The combined filtrates were concentrated under reduced pressure to afford a white solid. Recrystallization (CH_2Cl_2–hexane) afforded **65** (229 mg, 94%) as white crystals; mp 143–145 °C; R_f = 0.50 (MeOH–CH_2Cl_2, 1:9).

IR (ZnSe cell, film): 3293, 1560, 1505, 1393, 1318, 761 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.99 (s, 1 H), 7.05 (d, *J* = 7.6 Hz, 1 H), 6.97 (s, 1 H), 6.81 (d, *J* = 7.6 Hz, 1 H), 6.73 (t, *J* = 7.6 Hz, 1 H), 6.64 (t, *J* = 7.6 Hz, 1 H), 5.36 (s, 1 H), 3.86 (s, 2 H), 3.67 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 140.9 (C), 139.5 (C), 135.0 (CH), 133.0 (C), 121.7 (CH), 120.8 (CH), 120.2 (CH), 118.9 (CH), 101.5 (C), 43.4 (CH_2), 35.0 (CH_3).

LRMS (ESI+): *m*/*z* (%) = 201 ([M + H]$^+$, 100).

Method B: A magnetically stirred solution of imine **67** (350 mg, 1.76 mmol) in MeOH (8.5 mL) at 0 °C was treated, portionwise over 5 min, with $NaBH_4$ (136 mg, 3.51 mmol). The resulting mixture was warmed to r.t. and stirred for 1.5 h and treated carefully with H_2O (5 mL). Once H_2 evolution had ceased the MeOH was removed under reduced pressure and the resulting aqueous mixture extracted with EtOAc (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **65** (288 mg, 82%) as a white powder. This material was identical, in all respects, with that obtained via Method A described immediately above.

1-Methyl-1*H*-benzo[*b*]pyrazolo[4,3-*f*][1,4]oxazepine (67)

A magnetically stirred solution of pyrazole **55** (X = Cl, 500 mg, 3.46 mmol) and 2-aminophenol (1.13 g, 10.38 mmol) in DMF (4 mL) was treated with powdered KOH (388 mg, 6.92 mmol) and then heated at 120 °C for 2 h. The resulting mixture was cooled to r.t. then treated with sat. aq NH_4Cl (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (1 × 10 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The oil was subjected to flash column chromatography (silica gel, EtOAc–hexane, 1:4 → 1:1 gradient elution) and the relevant fractions were concentrated [R_f = 0.21 (EtOAc–hexane, 1:1)] to afford **67** (400 mg, 58%) as a brown oil.

IR (ZnSe cell, film): 1680, 1529, 1229, 1050, 895, 832, 760 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (s, 1 H), 7.23 (s, 1 H), 7.22 (d, *J* = 4.05 Hz, 1 H), 7.08 (m, 2 H), 7.88 (m, 1 H), 3.62 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.8 (C), 153.2 (C), 149.7 (CH), 138.8 (C), 137.1 (CH), 132.2 (CH), 128.4 (CH), 126.0 (CH), 120.2 (CH), 104.0 (C), 35.5 (CH_3).

LRMS (ESI+): *m*/*z* (%) = 200 ([M + H]$^+$, 100).

HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{10}N_3O$: 200.0824; found: 200.0818.

1-Methyl-4,5-dihydro-1*H*-benzo[*b*]pyrazolo[4,3-*f*][1,4]thiazepine (68)

A magnetically stirred solution of **55** (X = Cl, 150 mg, 1.0 mmol), 2-aminothiophenol (120 μL, 1.1 mmol), and piperidine (11 μL 0.1 mmol) in EtOH (5 mL) was heated at reflux for 3 h (TLC monitoring, no starting aldehyde **55** remained). The mixture was cooled to 0 °C and treated, in portions, with $NaBH_4$ (98 mg, 2.6 mmol, 2.5 equiv) and once all was dissolved, the mixture was reheated to reflux for 1 h then evaporated down to afford a yellow residue. This was dissolved in sat. $NaHCO_3$ soln (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow solid. The solid was subjected to flash column chromatography (silica gel, EtOAc–hexane, 3:7 → 8:2 gradient elution) and the relevant fractions were concentrated [R_f = 0.15 (EtOAc–hexane, 1:1)] to afford **68** (54 mg, 24%) as a white solid; mp 134–137 °C.

IR (ZnSe cell, film): 3358, 2937, 1479, 1417, 1312 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.37 (d, *J* = 7.8 Hz, 1 H), 7.29 (s, 1 H), 7.20 (dd, *J* = 7.8, 7.8 Hz, 1 H), 6.99 (d, *J* = 7.8 Hz, 1 H), 6.89 (dd, *J* = 7.8, 7.8 Hz, 1 H), 4.25 (s, 2 H), 3.83 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 152.1 (C), 137.5 (CH), 132.8 (C), 132.5 (CH), 130.9 (CH), 124.0 (CH), 123.9 (C), 123.3 (CH), 120.6 (C), 44.7 (CH_2), 36.5 (CH_3).

LRMS (ESI+): *m*/*z* (%) = 218 ([M + H]$^+$, 100).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{11}N_3NaS$: 240.0566; found: 240.0566.

2,2,2-Trifluoro-1-[1-methyl-1*H*-benzo[*b*]pyrazolo[4,3-*f*][1,4]thiazepin-5(4*H*)-yl]ethanone (69)

A magnetically stirred solution of compound **68** (200 mg, 920 μmol) and Et_3N (96 μL, 2.8 mmol) in THF (3 mL) at 0 °C was treated dropwise with TFAA (200 μL, 1.4 mmol). The resulting solution was allowed to stir at 0 °C for 3 h and then at r.t. for a further 18 h. The resulting mixture was then concentrated under reduced pressure to afford a yellow oil that was subjected to flash column chromatography (silica gel, EtOAc–hexane, 1:7). Concentration of the relevant fractions [R_f = 0.43 (EtOAc–hexane, 1:1] afforded **69** (262 mg, 91%) as a yellow solid; mp 115–118 °C.

IR (ZnSe cell, film): 2939, 1697, 1475, 1203, 1180, 1146 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.73 (d, *J* = 8 Hz, 1 H), 7.45–7.63 (m, 3 H), 7.40 (s, 1 H), 5.78 (d, *J* = 16 Hz, 1 H), 4.14 (d, *J* = 16 Hz, 1 H), 3.85 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 163.2 (C), 143.1 (CH), 133.7 (CH), 133.1 (CH), 132.0 (CH), 131.0 (CH), 129.8 (CH), 116.3 (C), 115.8 (CF_3), 46.4 (CH_2), 36.9 (CH_3).

LRMS (ESI+): *m*/*z* (%) = 314 ([M + H]$^+$, 100).

2,2,2-Trifluoro-1-[1-methyl-10-oxido-1*H*-benzo[*b*]pyrazolo[4,3-*f*][1,4]thiazepin-5(4*H*)-yl]ethanone (70)

A magnetically stirred solution of compound **69** (130 mg, 400 μmol) in glacial AcOH (1 mL) was treated dropwise with 30% aq H_2O_2 (40 μL, 400 μmol) at r.t. and then the mixture was heated to 80 °C for 2 h. The resulting solution was cooled to r.t. and treated with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. The oil was subjected to flash column chromatography (silica gel, EtOAc–hexane, 1:1) to afford two fractions, A and B.

Concentration of fraction A [R_f = 0.43 (EtOAc–hexane, 1:1)] afforded the starting compound **69** (17 mg, 13% recovery) as a yellow solid. This material was identical, in all respects, with an authentic sample.

Concentration of fraction B [R_f = 0.30 (EtOAc–hexane, 1:1)] afforded **70** (90 mg, 68%) as a yellow solid; mp 205–208 °C.

IR (ZnSe cell, film): 2924, 1707, 1477, 1209, 1149, 1057 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.97 (d, *J* = 7.8 Hz, 1 H), 7.83 (t, *J* = 7.8 Hz, 1 H), 7.69 (m, 2 H), 7.55 (s, 1 H), 5.90 (d, *J* = 17.2 Hz, 1 H), 4.29 (d, *J* = 17.2 Hz, 1 H), 4.15 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 156.3 (C), 140.1 (C), 139.7 (C), 139.3 (C), 138.2 (CH), 135.9 (CH), 131.9 (CH), 130.7 (CH), 121.4 (CH), 119.5 (CH), 115.7 (CF_3), 45.7 (CH_2), 37.9 (CH_3).

LRMS (ESI+): *m*/*z* (%) = 330 ([M + H]$^+$, 100).

1-Methyl-4,5-dihydro-1*H*-benzo[*b*]pyrazolo[4,3-*f*][1,4]thiazepine 10-Oxide (71)

A solution of acetamide **70** (90 mg, 273 μmol), and K_2CO_3 (100 mg, 720 μmol) in MeOH (6 mL) was stirred magnetically at r.t. for 18 h. The resulting mixture was then concentrated under reduced pressure followed by the addition of H_2O (15 mL), which was then extracted with EtOAc (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **71** (60 mg, 94%) as a white solid; mp 192–194 °C; R_f = 0.45 (MeOH–CH_2Cl_2, 1:9).

IR (ZnSe cell, film): 3302, 3096, 2928, 1547, 1468, 1029 cm^{-1}.

^{1}H NMR (200 MHz, MeOD-d_4): δ = 7.62 (d, *J* = 8.2 Hz, 1 H), 7.47 (s 1 H), 7.32 (t, *J* = 7.6 Hz, 1 H), 7.80 (m, 2 H), 4.77 (d, *J* = 15.6 Hz, 1 H), 4.29 (d, *J* = 15.6 Hz, 1 H), 4.03 (s, 3 H); the NH proton was not observed.

^{13}C NMR (75 MHz, CD_3OD): δ = 148.3 (C), 140.0 (C), 137.3 (CH), 135.3 (CH), 134.0 (CH), 123.0 (C), 121.5 (CH), 120.2 (C), 117.9 (CH), 38.0 (CH_3), 37.6 (CH_2).

LRMS (ESI+): *m*/*z* (%) = 234 ([M + H]$^+$, 100).

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd $C_{11}H_{11}N_3NaOS$: 256.0515; found: 256.0515.

2,2,2-Trifluoro-1-[1-methyl-10,10-dioxido-1*H*-benzo[*b*]pyrazolo[4,3-*f*][1,4]thiazepin-5(4*H*)-yl]ethanone (72)

A magnetically stirred solution of compound **69** (50 mg, 160 μmol) in glacial AcOH (0.6 mL) was treated dropwise with 30% aq H_2O_2 (50 μL, 480 μmol) at r.t. and then heated to 80 °C for 4 h. The resulting solution was cooled to r.t. and treated with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **72** (55 mg, 80%) as a yellow solid, mp 187–190 °C; R_f = 0.25 (EtOAc–hexane, 1:1).

IR (ZnSe cell, film): 3100, 2961, 1710, 1478, 1366, 1211, 1167 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 8.18 (dd, *J* = 1.4, 7.8 Hz, 1 H), 7.93 (dt, *J* = 1.2, 7.8 Hz, 1 H), 7.80 (dt, *J* = 1.4, 7.9 Hz, 1 H), 7.76 (dd, *J* = 1.2, 7.9 Hz, 1 H), 7.5 (s, 1 H), 5.93 (d, *J* = 17.2 Hz, 1 H), 4.36 (d, *J* = 17.2 Hz, 1 H), 4.20 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 157.9 (C), 157.5 (C), 141.2 (C), 137.5 (CH), 137.3 (CH), 131.9 (CH), 131.4 (CH), 128.6 (CH), 118.9 (C), 116–118 (CF_3, unresolved), 46.0 (CH_2), 40.6 (CH_3).

LRMS (ESI+): *m*/*z* (%) = 346 ([M + H]$^+$, 100).

1-Methyl-4,5-dihydro-1*H*-benzo[*b*]pyrazolo[4,3-*f*][1,4]thiazepine 10,10-Dioxide (73)

A solution of acetamide **72** (56 mg, 159 μmol), and K_2CO_3 (62 mg, 450 μmol) in MeOH (4 mL) was stirred magnetically at r.t. for 18 h. The resulting mixture was then concentrated under reduced pressure followed by the addition of H_2O (15 mL) which was then extracted with EtOAc (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **73** (39 mg, 97%) as a white solid; mp 172–174 °C; R_f = 0.39 (MeOH–CH_2Cl_2, 1:9).

IR (ZnSe cell, film): 3398, 3078, 2958, 1602, 1447, 1312, 1164 cm^{-1}.

^{1}H NMR (200 MHz, MeOD-d_4): δ = 7.80 (d, J = 8.4 Hz, 1 H), 7.45 (s 1 H), 7.29 (t, J = 7.0 Hz, 1 H), 7.69 (m, 2 H), 4.57 (s, 2 H), 4.11 (s, 3 H); the NH proton was not observed.

^{13}C NMR (75 MHz, CD_3OD): δ = 146.0 (C), 140.0 (C), 137.0 (CH), 135.6 (CH), 126.8 (CH), 122.6 (C), 120.9 (CH), 117.1 (C), 116.7 (CH), 38.8 (CH_2), 38.5 (CH_3).

LRMS (ESI+): m/z (%) = 250 ([M + H]$^+$, 100).

HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{11}H_{11}N_3O_2NaS$: 272.0454; found: 272.0464.

1,2-Bis(2-nitrophenyl)ethane (76)

A magnetically stirred solution of pyrazole **55** (X = Cl, 500 mg, 3.46 mmol) and 2-nitrotoluene (1.42 g, 10.38 mmol) in DMF (4 mL) was treated with powdered KOH (388 mg, 6.92 mmol) and then heated at 120 °C for 2 h. The resulting mixture was cooled to r.t. then treated with sat. aq NH_4Cl (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (1 × 10 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The residue was subjected to flash column chromatography (silica gel, EtOAc–hexane, 1:4 → 1:1 gradient elution) to afford two fractions, A and B.

Concentration of fraction A [R_f = 0.65 (EtOAc–hexane, 1:1)] afforded the starting pyrazole **55** (462 mg, 92% recovery) as yellow crystals. This material was identical, in all respects, with an authentic sample.

Concentration of fraction B [R_f = 0.35 (EtOAc–hexane, 1:1)] afforded **76** (1.24 g, 88%) as a white solid. The spectral data was identical, in all respects, with those previously reported.[26]

(*E*)-5-Chloro-1-methyl-4-(2-nitrostyryl)-1*H*-pyrazole (77)

A magnetically stirred solution of pyrazole **55** (X = Cl, 500 mg, 3.46 mmol) and 2-nitrotoluene (1.42 g, 10.38 mmol) in DMF (4 mL) was treated with powdered KOH (388 mg, 6.92 mmol) then stirred at r.t. for 18 h. The resulting mixture was treated with sat. aq NH_4Cl (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (1 × 10 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The residue was subjected to flash column chromatography (silica gel, EtOAc–hexane, 1:4 → 1:1 gradient elution) and the relevant fractions were concentrated [R_f = 0.57 (EtOAc–hexane, 1:1)] to afford **77** (675 mg, 74%) as a yellow solid; mp 71–73 °C.

IR (ZnSe cell, film): 1635, 1604, 1519, 1475, 1389, 1343, 1254, 956, 785, 741 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, J = 7.5 Hz, 1 H), 7.65 (s 1 H), 7.64 (d, J = 5.4 Hz, 1 H), 7.52 (t, J = 6.9 Hz, 1 H), 7.35 (d, J = 16.3 Hz, 1 H), 7.31 (d, J = 6.9 Hz, 1 H), 6.75 (d, J = 16.3 Hz, 1 H), 3.77 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.7 (C), 137.1 (CH), 133.0 (CH), 128.3 (C), 127.8 (CH), 127.7 (CH), 126.3 (C), 124.8 (CH), 122.4 (CH), 121.9 (CH), 116.4 (C), 36.4 (CH_3).

LRMS (ESI+): m/z (%) = 264 ([M + H]$^+$, 100).

HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{12}H_{11}{}^{35}ClN_3O_2$: 264.0540; found: 264.0534.

Ethyl 5-Chloro-2-[(2,6-dichloro-5-nitropyrimidin-4-yl)amino]benzoate (90)

A magnetically stirred solution of 2,4,6-trichloro-5-nitropyrimidine (**89**, 1.33 g, 5.81 mmol) and DIPEA (1.30 mL, 7.74 mmol) in anhyd 1,4-dioxane (15 mL) at r.t. was treated dropwise with a solution of ethyl 2-amino-5-chlorobenzoate (**87**, 776 mg, 3.87 mmol) in anhyd 1,4-dioxane (5 mL). The resulting solution was heated to 50–55 °C and stirred for 3 h then cooled to r.t. and concentrated under reduced pressure. The residue was subjected to flash column chromatography (silica gel, EtOAc–hexane, 1:30) and the relevant fractions were concentrated [R_f = 0.60 (hexane–CH_2Cl_2, 1:3)] to afford **90** (500 mg, 33%) as a yellow solid; mp 83–85 °C.

IR (ZnSe cell, film): 3548, 2902, 1695, 1561, 1536, 1468, 1304, 1247, 1204, 1077, 1011, 783 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.0 (s, 1 H), 8.46 (d, J = 9.0 Hz, 1 H), 8.07 (d, J = 2.7 Hz, 1 H), 7.59 (dd, J = 2.7, 9.2 Hz, 1 H), 4.46 (q, J = 6.9 Hz, 2 H), 1.44 (t, J = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7 (C), 159.4 (C), 155.2 (C), 153.5 (C), 137.4 (C), 134.0 (CH), 131.1 (CH), 130.2 (C), 123.9 (CH), 119.9 (C), 62.7 (CH_2), 14.3 (CH_3); one unresolved quaternary carbon.

LRMS (ESI+): m/z (%) = 391/393/395 ([M + H]$^+$, 100/96/27).

2,4,8-Trichloro-5,11-dihydro-6*H*-benzo[*e*]pyrimido[5,4-*b*][1,4]diazepin-6-one (92)

A magnetically stirred suspension of compound **90** (359 mg, 0.916 mmol) and Fe powder (512 mg, 9.16 mmol) in glacial AcOH (14 mL) was heated at 130 °C in a sealed tube for 20 h. The cooled mixture was and treated with H_2O (20 mL) and the aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **92** (273 mg, 94%) as a yellow solid; mp 272–274 °C; R_f = 0.15 (hexane–CH_2Cl_2, 1:5).

IR (ZnSe, solid): 3337, 3252, 3184, 3106, 2927, 1647, 1532, 1459, 1254, 1219, 1142 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.16 (br s, 1 H), 7.72 (d, J_1 = 2.4 Hz, 1 H), 7.53 (dd, J = 2.2, 8.8 Hz, 1 H), 7.18 (d, J = 8.8 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.9 (C), 159.7 (C), 151.6 (C), 150.1 (C), 142.0 (C), 133.8 (CH), 131.6 (CH), 126.8 (C), 123.0 (C), 122.2 (CH), 117.4 (C).

LRMS (APCI+): m/z (%) = 315/317/319/321 ([M + H]$^+$, 94/100/33/24).

HRMS (APCI+): m/z [M + H]$^+$ calcd for $C_{11}H_6{}^{37}Cl_3N_4O$: 320.9519; found: 320.9727.

Ethyl 2-[(2,6-Dichloro-5-nitropyrimidin-4-yl)oxy]benzoate (91) and Ethyl 2-[(5-Amino-2,6-dichloropyrimidin-4-yl)oxy]benzoate (93)

Step ii: A magnetically stirred solution of 2,4,6-trichloro-5-nitropyrimidine (**89**, 1.68 g, 7.36 mmol) and DIPEA (1.72 mL, 9.81 mmol) in anhyd 1,4-dioxane (20 mL) at r.t. was treated dropwise with a solution of ethyl 2-hydroxybenzoate (**88**, 722 μL, 4.91 mmol) in 1,4-dioxane (10 mL). The resulting mixture was stirred at r.t. for 4 h then diluted with EtOAc (150 mL) and washed with brine (2 × 50 mL) and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **91** as an orange solid [R_f = 0.56 (EtOAc–hexane, 1:5)]. This material was subjected to the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz, acetone-d_6): δ = 8.12 (d, J = 7.6 Hz, 1 H), 7.81 (dd, J = 7.2 Hz, 1 H), 7.57 (dd, J = 7.7 Hz, 1 H), 7.46 (d, J = 8.4 Hz, 1 H), 4.24 (q, J = 6.9 Hz, 2 H), 1.20 (t, J = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 164.4 (C), 163.4 (C), 159.2 (C), 154.1 (C), 151.0 (C), 135.6 (CH), 133.0 (CH), 128.6 (CH), 128.0 (C), 124.4 (CH), 124.0 (C), 62.2 (CH_2), 14.1 (CH_3).

Step iv: A magnetically stirred suspension of compound **91** (from the previous step) and Fe powder (2.73 g, 48.9 mmol) in glacial AcOH (60 mL) was heated at 60 °C for 18 h. The resulting mixture was filtered through Celite and the solids thus retained were washed with acetone. The filtrate was then concentrated under reduced pressure and treated with ice-cold water resulting in a brown precipitate that was then filtered, and washed further with ice-cold water. The solid was then dried under reduced pressure to afford **93** (1.61

g, 100% over 2 steps) as a brown solid; mp 82–83 °C; R_f = 0.39 (EtOAc–hexane, 1:5).

IR (solid): 3467, 3351, 1728, 1607, 1404, 1240, 1206, 1075, 958, 871 cm^{-1}.

^1H NMR (500 MHz, acetone-d_6): δ = 8.04 (dd, J = 1.6, 7.8 Hz, 1 H), 7.74 (ddd, J = 1.6, 7.8, 7.8 Hz, 1 H), 7.45 (dd, J = 7.6, 7.6 Hz, 1 H), 7.39 (d, J = 8.2 Hz, 1 H), 5.41 (br s, 2 H), 4.17 (q, J = 7.1 Hz, 2 H), 1.14 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 165.0 (C), 161.9 (C), 159.3 (C), 152.3 (C), 143.1 (C), 141.2 (C), 135.0 (CH), 132.7 (CH), 128.0 (C), 127.3 (CH), 125.0 (CH), 61.8 (CH_2), 14.1 (CH_3).

LRMS (APCI+): m/z (%) = 328/330 ([M + H]$^+$, 100/62).

2,4-Dichlorobenzo[*f*]pyrimido[4,5-*b*][1,4]oxazepin-6(5*H*)-one (94)

A magnetically stirred solution of compound **93** (67 mg, 0.203 mmol) in CH_2Cl_2 (2 mL) at 0 °C was treated dropwise with 2.0 M Me_3Al in toluene (162 μL, 0.325 mmol). The resulting mixture was stirred at this temperature for 0.5 h and then warmed to r.t. and stirred for a further 1 h. The mixture was then heated at reflux and stirred for a further 18 h. The cooled mixture was then treated with 1 M aq HCl (1 mL) and the separated organic phase was concentrated under reduced pressure. The residue was subjected to flash column chromatography (silica gel, hexane–CH_2Cl_2, 1:2 → 1:4, gradient elution) and the relevant fractions were concentrated [R_f = 0.55 (10% ammonia in MeOH–CH_2Cl_2, 1:10)] to afford **94** (47 mg, 82%) as a brown solid; mp >260 °C (dec.).

IR (ZnSe cell, solid): 3176, 3086, 2919, 1683, 1455, 1410, 1331, 1131 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 10.65 (s, 1 H), 7.83 (d, J = 7.8 Hz, 1 H), 7.70 (ddd, J = 1.5, 7.8, 7.8 Hz, 1 H), 7.43 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.6 (C), 163.8 (C), 155.5 (C), 153.4 (C), 151.5 (C), 135.2 (CH), 131.8 (CH), 126.9 (CH), 124.3 (C), 122.7 (C), 121.2 (CH).

LRMS (APCI+): m/z (%) = 282/284 ([M + H]$^+$, 100/74).

Anal. Calcd for $C_{11}H_5Cl_2N_3O_2$: C, 46.84; H, 1.79; N, 14.90. Found: C, 46.83; H, 2.35; N, 14.40.

2-[(2-Chloro-5-nitropyrimidin-4-yl)amino]benzaldehyde (100)

2,4-Dichloro-5-nitropyrimidine (**97**, 100 mg, 0.52 mmol) and DIPEA (120 μL, 0.69 mmol) in anhyd 1,4-dioxane (1.8 mL) were treated with 2-aminobenzaldehyde (**98**, 42 mg, 0.34 mmol) and the mixture was stirred at 50–55 °C for 2 h. The resulting mixture was concentrated under reduced pressure and the residue subjected to flash column chromatography (silica gel, EtOAc–hexane, 1:20 → 1:10 gradient elution). Concentration of the relevant fractions [R_f = 0.30 (EtOAc–hexane, 1:5)] afforded **100** (74 mg, 78%) as a yellow-orange solid; mp 208–209 °C.

IR (solid): 3389, 2932, 1675, 1577, 1555, 1451, 1366, 1313, 1253, 1221, 1195 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 12.92 (s, 1 H), 10.04 (s, 1 H), 9.25 (s, 1 H), 8.82 (d, J = 8.3 Hz, 1 H), 7.82 (d, J = 7.3 Hz, 1 H), 7.74 (dd, J = 7.5 Hz, 1 H), 7.43 (dd, J = 7.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.3 (CH), 163.6 (C), 157.8 (C), 153.5 (C), 137.9 (C), 136.4 (CH), 135.6 (CH), 127.9 (CH), 125.6 (CH), 124.7 (C), 122.7 (CH).

LRMS (APCI+): m/z (%) = 285/281/279 ([M + H]$^+$, 28/35/100).

2-[(2-Chloro-5-nitropyrimidin-4-yl)oxy]benzaldehyde (101)

A magnetically stirred solution of 2,4-dichloro-5-nitropyrimidine (**97**, 100 mg, 0.52 mmol) and DIPEA (120 μL, 0.69 mmol) in anhyd 1,4-dioxane (1.8 mL) was treated dropwise with 2-hydroxybenzaldehyde (**99**, 36 μL, 0.34 mmol). The resulting mixture was stirred at 50 °C for 1.6 h followed by 3 h at r.t. and then concentrated under reduced pressure. The resulting residue was subjected to flash column chromatography (silica gel, EtOAc–hexane, EtOAc–hexane, 1:10) and the relevant fractions were concentrated [R_f = 0.20 (EtOAc–hexane, 1:4)] to afford **101** (70 mg, 73%) as a red/black solid; mp 130–132 °C.

IR (solid): 3078, 2880, 2761, 1695, 1587, 1555, 1415, 1331, 1291, 1201, 1100, 962, 849 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 10.02 (s, 1 H), 9.22 (s, 1 H), 7.94 (dd, J = 1.7, 7.8 Hz, 1 H), 7.75 (ddd, J = 1.7, 7.8, 7.8 Hz, 1 H), 7.56 (ddd, J = 0.7, 7.6, 7.6 Hz, 1 H), 7.31 (d, J = 8.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.7, 162.9, 162.2, 157.6, 150.7, 135.9, 133.6, 131.5, 127.8, 123.3; one unresolved quaternary carbon.

LRMS (APCI+): m/z (%) = 282, 280 ([M + H]$^+$, 60/67).

2-Chloro-6,11-dihydro-5*H*-benzo[*e*]pyrimido[5,4-*b*][1,4]diazepine (95)

A magnetically stirred solution of compound **100** (48 mg, 0.17 mmol) and PtO_2 (1.2 mg, 5 μmol) in MeOH (1.5 mL) under an atmosphere of H_2 (1 atm) was heated at reflux for 18 h. The resulting mixture was filtered through Celite and the solids thus retained were washed with EtOAc (3 × 5 mL). The combined filtrates were concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel, EtOAc–hexane, EtOAc–hexane, 1:4). Concentration of the relevant fractions [R_f = 0.46 (EtOAc–hexane, 1:2)] afforded **95** (13 mg, 34%) as a brown powder; mp >155 °C dec.

IR (solid): 3352, 3255, 3045, 2925, 2856, 1704, 1574, 1537, 1495, 1395, 1279, 1228, 1157, 1121, 1051, 982 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.68 (s, 1 H), 7.19 (ddd, J = 1.5, 7.7, 7.7 Hz, 1 H), 7.07 (m, 2 H), 6.92 (ddd, ^3J = 0.9, 7.5, 7.5 Hz, 1 H), 4.17 (s, 2 H); NH signal not observed.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.8 (C), 151.3 (C), 143.9 (CH), 141.1 (C), 132.6 (C), 129.8 (CH), 129.6 (C), 129.3 (CH), 123.2 (CH), 120.4 (CH), 51.8 (CH_2).

LRMS (APCI+): m/z (%) = 235, 233 ([M + H]$^+$, 27/100).

HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{11}H_9{}^{37}ClN_4Na$: 257.0384; found: 257.0378.

2-Chloro-5,6-dihydrobenzo[*f*]pyrimido[4,5-*b*][1,4]oxazepine (96)

A magnetically stirred solution of compound **101** (74 mg, 0.265 mmol) and PtO_2 (1.8 mg, 8 μmol) in MeOH (2.3 mL) under an atmosphere of H_2 (1 atm) was heated at reflux for 18 h. The resulting mixture was filtered through Celite and the solids thus retained were washed with solvent MeOH–EtOAc (1:20, 3 × 5 mL). The combined filtrates were concentrated under reduced pressure and the residue was purified by flash column chromatography (silica gel, MeOH–EtOAc–hexane, 0.1:10:30). Concentration of the relevant fractions [R_f = 0.46 (EtOAc–hexane, 1:2)] afforded **96** (25 mg, 40%) as a white powder; mp 191–193 °C.

IR (solid): 3365, 2922, 1579, 1547, 1483, 1428, 1358, 1340, 1208, 1170, 1107, 1040, 938 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.97 (s, 1 H), 7.35 (d, J = 7.5 Hz, 1 H), 7.28 (d, J = 7.0 Hz, 1 H), 7.24 (d, J = 8.0 Hz, 1 H), 7.18 (d, J = 7.0 Hz, 1 H), 4.44 (s, 2 H); NH signal not observed.

^{13}C NMR (125 MHz, CD_3OD): δ = 157.2 (C), 156.4 (C), 148.6 (CH), 147.2 (C), 134.9 (C), 132.3 (CH), 130.6 (CH), 129.7 (CH), 126.7 (C), 121.8 (CH), 46.9 (CH_2).

LRMS (APCI+): m/z (%) = 237, 234 ([M + H]$^+$, 27/100).

HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{11}H_9{}^{35}ClN_3O$: 234.0434; found: 234.0429.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) *Comprehensive Heterocyclic Chemistry II*; Vol. 9; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier: Oxford, **1996**.
(2) Carraher, C. E. *J. Chem. Educ.* **1978**, *55*, 51.
(3) Tucker, H.; Le Count, D. J. *1,4-Azepines*, In *Comprehensive Heterocyclic Chemistry II*; Vol. 9; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier: Oxford, **1996**, 152.
(4) Kozikowski, A. P.; Greco, M. N. *J. Org. Chem.* **1984**, *49*, 2310.
(5) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4335.
(6) Thiele, J.; Holzinger, O. *Justus Liebigs Ann. Chem.* **1899**, *305*, 96.
(7) (a) Schindler, W. US 2,948,718, **1960**. (b) Schindler, W. DE 2,011,087, **1970**.
(8) Sternbach, L. H.; Fryer, R. I.; Metlesics, W.; Reeder, E.; Sach, G.; Saucy, G.; Stempel, A. *J. Org. Chem.* **1962**, *27*, 3788.
(9) van der Burg, W. J. US 4,145,434, **1977**.
(10) Kemperman, G. J.; Stuk, T. L.; van der Linden, J. J. M. WO 2008,003,460, **2009**.
(11) Cockerill, G. S.; Kocienski, P.; Treadgold, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2093.
(12) Yamamoto, K.; Yamazaki, S. *Thiepanes and Thiepines*, In *Comprehensive Heterocyclic Chemistry II*; Vol. 9; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier: Oxford, **1996**, 67.
(13) Griebel, G.; Perrault, G.; Tan, S.; Schoemaker, H.; Sanger, D. J. *Behav. Pharmacol.* **1999**, *10*, 483.
(14) Zirkle, C. L.; Pa, B. US 3,609,167, **1971**.
(15) Frauenrath, H. *1,3-Dioxepanes, 1,3-Oxathiepanes, and 1,3-Dithiepanes*, In *Comprehensive Heterocyclic Chemistry II*; Vol. 9; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier: Oxford, **1996**, 236.
(16) Frauenrath, H. *1,4-Dioxepanes, 1,4-Oxathiepanes, and 1,4-Dithiepanes*, In *Comprehensive Heterocyclic Chemistry II*; Vol. 9; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier: Oxford, **1996**, 271.
(17) Kowalski, P.; Mitka, K.; Ossowska, K.; Kolarska, Z. *Tetrahedron* **2005**, *61*, 1933.
(18) (a) Ring, R. H.; Schechter, L. E.; Leonard, S. K.; Dwyer, J. M.; Platt, B. J.; Graf, R.; Grauer, S.; Pulicicchio, C.; Resnick, L.; Rahman, Z.; Sukoff Rizzo, S. J.; Luo, B.; Beyer, C. E.; Logue, S. F.; Marquis, K. L.; Hughes, Z. A.; Rosenzweig-Lipson, S. *Neuropharmacology* **2010**, *58*, 69. (b) Hicks, C.; Jorgensen, W.; Brown, C.; Fardell, J.; Koehbach, J.; Gruber, C. W.; Kassiou, M.; Hunt, G. E.; McGregor, I. S. *J. Neuroendocrinol.* **2012**, *24*, 1012.
(19) Rahman, Z.; Resnick, L.; Rosenzweig-Lipson, S. J.; Ring, R. H. US 2007,0,117,794, **2007**.
(20) McGregor, I. S.; Callaghan, P. D.; Hunt, G. E. *Brit. J. Pharmacol.* **2008**, *154*, 358.
(21) Frantz, M.-C. L.; Rodrigo, J.; Boudier, L.; Durroux, T.; Mouillac, B.; Hibert, M. *J. Med. Chem.* **2010**, *53*, 1546.
(22) Hudson, P.; Pitt, G.; Batt, R.; Roe, M. WO 2005,023,812, **2005**.
(23) Abd El Latif, F. M. *J. Heterocycl. Chem.* **2000**, *37*, 1659.
(24) Park, M. S.; Park, H. J.; Park, K. H.; Lee, K. I. *Synth. Commun.* **2004**, *34*, 1541.
(25) Potapov, A. S.; Chernova, N. P.; Ogorodnikov, V. D.; Petrenko, T. V.; Khlebnikov, A. I. *Beilstein J. Org. Chem.* **2011**, *7*, 1526.
(26) (a) Russell, G. A.; Janzen, E. G. *J. Am. Chem. Soc.* **1967**, *89*, 300. (b) Gandhi, S. S.; Gibson, M. S.; Kaldas, M. L.; Vines, S. M. *J. Org. Chem.* **1979**, *44*, 4705.
(27) Paisán-Ruíz, C.; Jain, S.; Evans, E. W.; Gilks, W. P.; Simón, J.; van der Brug, M.; de Munain, A. L.; Aparicio, S.; Gil, A. M.; Khan, N.; Johnson, J.; Martinez, J. R.; Nicholl, D.; Carrera, I. M.; Peňa, A. S.; de Silva, R.; Lees, A.; Martí-Massó, J. F.; Pérez-Tur, J.; Wood, N. W.; Singleton, A. B. *Neuron* **2004**, *44*, 595.
(28) West, A. B.; Moore, D. J.; Biskup, S.; Bugayenko, A.; Smith, W. W.; Ross, C. A.; Dawson, V. L.; Dawson, T. M. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 16842.
(29) Deng, X.; Dzamko, N.; Prescott, A.; Davies, P.; Liu, Q.; Yang, Q.; Lee, J.-D.; Patricelli, M. P.; Nomanbhoy, T. K.; Alessi, D. R.; Gray, N. S. *Nat. Chem. Biol.* **2011**, *7*, 203.