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Synthesis of *N*-substituted dibenzoazepine–pyridazine derivatives as potential neurologically active drugs

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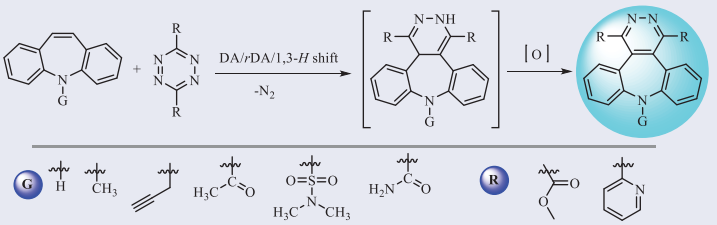
ABSTRACT

Syntheses of pyridazine derivatives of dibenzoazepine, starting from *N*-substituted-dibenzoazepines, are reported here for the first time. In the reaction sequence, *N*-substitute dibenzoazepine derivatives were synthesized and then, examined *inverse* electron demand Diels–Alder (IEDDA) reactions between *N*-substituted dibenzoazepine derivatives and tetrazines. While in some reactions, targeted products were obtained using phenyliodo-bis(trifluoroacetate) (PIFA), in other reactions, they were obtained directly with tetrazines which also behaved as the oxidizing agent. Structures of these compounds were fully characterized by NMR, IR, and HRMS spectroscopic techniques.

GRAPHICAL ABSTRACT



- *Novel 12 dibenzoazepine-pyridazine hybrid skeletons*
- *Easy syntheses*
- *Yield up to 98%*
- *Potential biological and pharmacologically active skeletons*

ARTICLE HISTORY
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KEYWORDS
Azepine; 5*H*-dibenzo[*b*,*f*]azepine; iminostilbene; *inverse* electron demand Diels–Alder; PIFA; pyridazine; tetrazine

Introduction

Nitrogeneous heterocyclic aromatic compounds are an important class of organic compounds, due to their physical, chemical, and biological properties arising both from their reactivity and stability.[1,2] These species are used in several applications such as the pharmaceutical industries and in agrochemical researches. Tricyclic heteroaromatic compounds containing nitrogen atoms have become attractive targets for synthetic chemists due to their biological and pharmacological activities, and their structural

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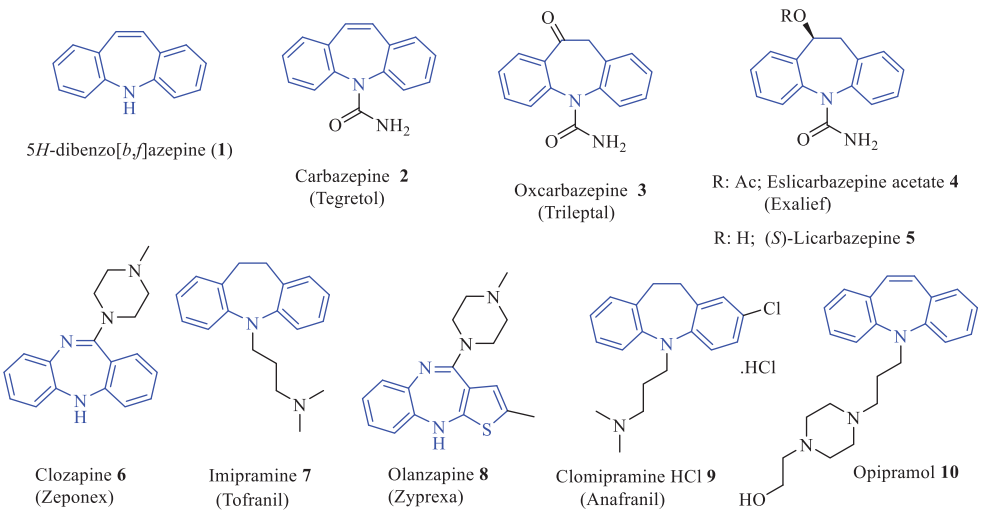
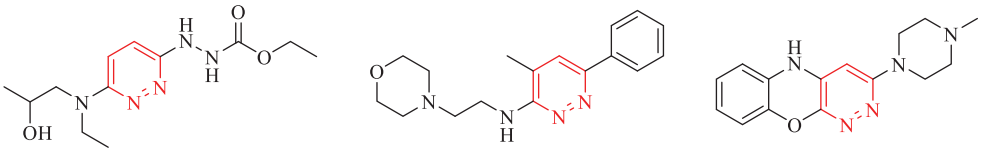


Figure 1. Some pharmaceutically important derivatives of dibenzoazepine **1**.

diversity.[3–5] The 5*H*-dibenzo[*b*,*f*]azepine (**1**), commonly known as iminostilbene, and which contains a seven-membered ring, is a very common tricyclic amine used as an intermediate or starting compound in the synthesis of anticonvulsant drugs (Fig. 1).[6] Additionally, the 5*H*-dibenzo[*b*,*f*]azepine (**1**) nucleus forms the main skeleton of medicinal and pharmacologically important antidepressant drug structures that are particularly effective in the central nervous system.[7] These anticonvulsant or antiepileptic drugs are used in the treatment of epilepsy, chizophrenia, panic attack, etc. one of the common chronic neurological disorders, in bipolar disorders and in the prevention of neuropathic pain.[8] Dibenzoazepine and its derivatives possess a remarkably broad spectrum of pharmacological activities including antidepressant, antiallergic, antihistamine, spasmolytic, seratonin antagonistic, anticonvulsive, antiemetic, antiepileptic, anti-inflammatory, sedative, and fungicidal activity.[9] Carbamazepine **2** and oxcarbazepine **3** (*Trileptal*) started to be used under the trade name *Tegretol* and belongs to a group of drugs called 'antiepileptics' (Fig. 1).[10] Many of the drugs that activate the central nervous system, such as carbazepine **2**, imipramine **7**, clomipramine HCl **9**, and opipranol **10**, have tricyclic dibenzoazepine **1** core and its 10-11 dihydro version (Fig. 1).[9] Eslicarbazepine acetate **4** (Zebinix), (*S*)-Licarbazepine **5**, Clozapine **6** (clozaryl), Imipramine **7** (Tofranil), Olanzapine **8**, Clomipramine HCl **9** and Opipramol **10** belong to a type of antipsychotic drug group known as tricyclic antidepressants (Fig. 1).[11] In addition, the dibenzoazepine **1** is widely used in materials chemistry, as an organic field-effect transistors (OFET), a light emitting diodes (OLED), and hole transport material due to their electron donor properties.[12,13] On the other hand, diazine scaffold containing two sp^2-hybridized adjacent nitrogen atoms is very important classes of six-membered heterocyclic compounds. Pyridazines are a family of diazine compounds and they have a wide application in medicine, pharmacy, cosmetics, and agriculture.[14] The pyridazine core is a part of the structure of some therapeutic agents such as cadralazine **11**, minaprine **12**, pipofezine **13**, etc. commercially on the market (Fig. 2).[15,16]



Cadralazine **11** Minaprine **12** Pipofezine **13**

Figure 2. Structure of some pyridazine-based drugs.

To generate new pyridazine-based bioactive cores, the conversion of the tetrazine unit into pyridazine-derivatives is an extremely advantageous method.[17] With the above considerations in mind, as part of biologically and pharmaceutically active dibenzoazepine and diazine, we decided to synthesize novel dibenzoazepine–pyridazine derivatives and developed a strategy that engaged the *N*-substitute-dibenzoazepines with tetrazines in an *inverse* electron demand Diels–Alder reaction (IEDDA) to give the corresponding the dibenzoazepine–pyridazine hybrid derivatives.

Results and discussions

The IEDDA reaction is a cycloaddition between highest occupied molecule orbital (HOMO) energy of an electron-rich dienophile and lowest un-occupied molecular orbital (LUMO) energy of an electron-poor diene.[18] IEDDA reactions between *s*-tetrazines and olefins are very common procedures to generate pyridazine skeletons.[19] These reactions conclusion in the formation of bicyclic intermediates via nitrogen elimination readily and then rearranging, giving dihydropyridazines that can be oxidized to pyridazines.[20]

Here, we examined the IEDDA reactions between *N*-substituted dibenzoazepine derivatives **1–2** and **14–17** and tetrazines, dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (DET) (**18**) and 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (DPT) (**19**). 5*H*-dibenzo[*b*,*f*]azepine (**1**), which was commercially available, became the key structure that allowed us to afford *N*-substituted dibenzoazepine derivatives **1–2** and **14–17** (Fig. 3).

Dibenzoazepine derivatives 5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide (**2**),[21] 5-methyl-5*H*-dibenzo[*b*,*f*]azepine (**14**),[22] 5-(prop-2-yn-1-yl)-5*H*-dibenzo[*b*,*f*]azepine (**15**),[23] and 1-(5*H*-dibenzo[*b*,*f*]azepin-5-yl)ethan-1-one (**16**)[10] were synthesized according to a previously reported methods. Treatment of *N*,*N*-dimethylsulfamoyl chloride with pyridine in toluene at 80 °C for 1 h followed by the addition of 5*H*-dibenzo[*b*,*f*]azepine (**1**) gave *N*,*N*-dimethyl-5*H*-dibenzo[*b*,*f*]azepine-5-sulfonamide (**17**) in 96% yield.

Following the same sequence of Diels–Alder (DA), of *retro*-Diels–Alder (*r*DA), and of 1,3-prototropic *H*-shifting reactions (Scheme 1), the adducts **20–27** were obtained when the electron-rich dienophile *N*-substituted dibenzoazepine derivatives **1–2** and **4–15** were reacted with tetrazines **18** and **19** (1.1 equiv.) in a sealed tube in dry toluene at 110–180 °C for 12–72 h (Scheme 2). Then, the cycloadducts **20–27** was used directly in the next reaction without requiring separation and oxidized with PIFA to access to target products **28–35** in dry methylene chloride in excellent yields (74–98%).

As known, the IEDDA reaction is a cycloaddition between HOMO energy of an electron-rich dienophile and LUMO energy of an electron-poor diene. Electron-

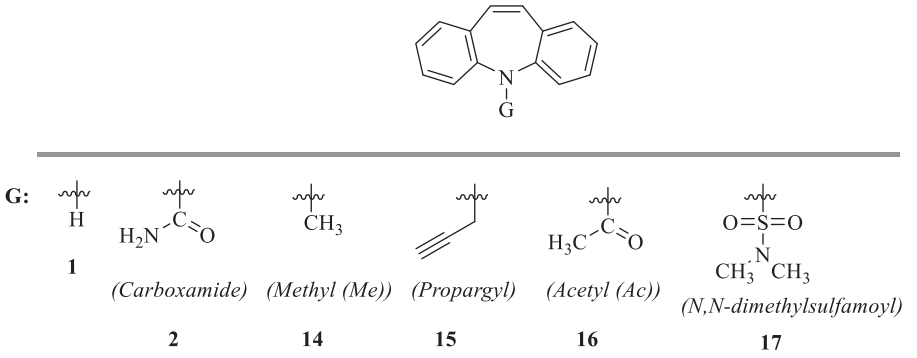
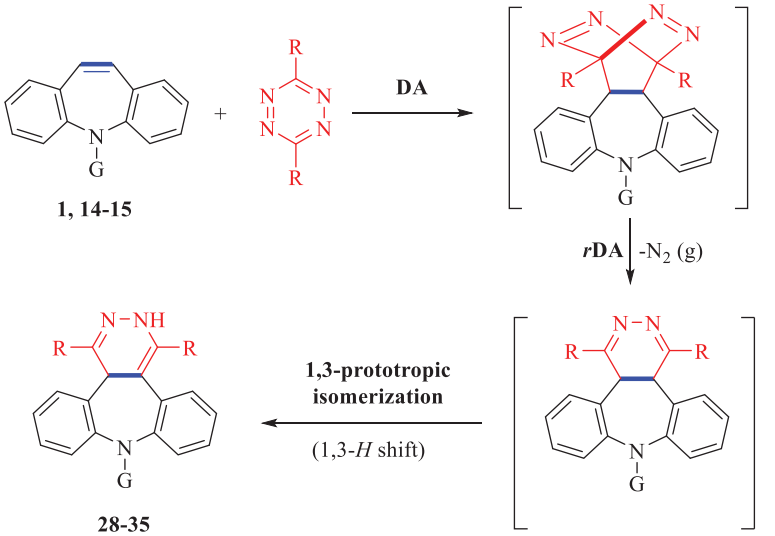
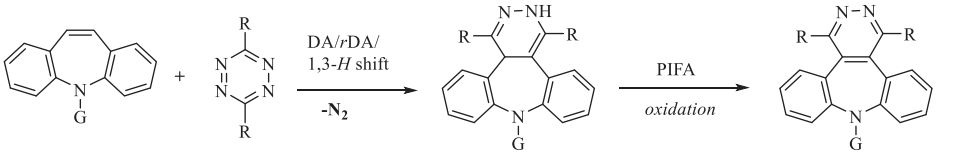


Figure 3. *N*-substituted dibenzoazepine derivatives.



Scheme 1. Route of synthesis of *N*-substituted dibenzoazepine-pyridazine derivatives **28–35**.



1, G= H
14, G= Me
15, G= Propargyl
16, G= Carboxamide

18, R= CO_2Me
19, R= 2-Py

20, G= H, R= CO_2Me
21, G= Me, R= CO_2Me
22, G= Propargyl, R= CO_2Me
23, G= Carboxamide, R= CO_2Me
24, G= H, R= 2-Py
25, G= Me, R= 2-Py
26, G= Propargyl, R= 2-Py
27, G= Carboxamide, R= 2-Py

28, G= H, R= CO_2Me
29, G= Me, R= CO_2Me
30, G= Propargyl, R= CO_2Me
31, G= Carboxamide, R= CO_2Me
32, G= H, R= 2-Py
33, G= Me, R= 2-Py
34, G= Propargyl, R= 2-Py
35, G= Carboxamide, R= 2-Py

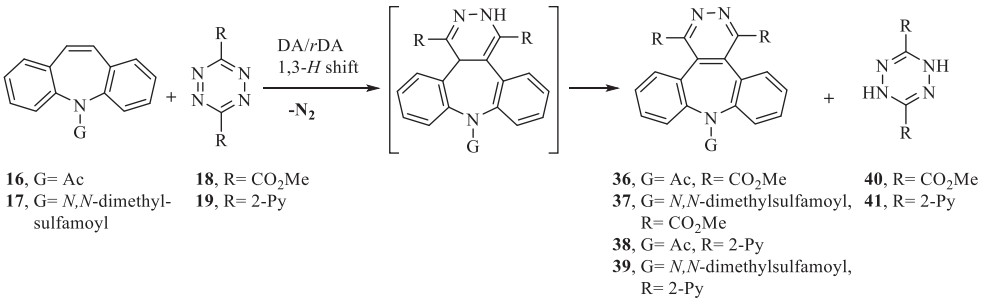
Scheme 2. Synthesis mechanism of **28–35** via the IEDDA reaction.

withdrawing groups (EWGs) decrease both HOMO and LUMO energy of the cycloaddends while electron-donating groups (EDGs) increase both HOMO and LUMO energy. Therefore, the adducts **20–27** were obtained via IEDDA reactions of the electron-rich

Table 1. Synthesis of **28–39** from *N*-substituted dibenzoazepine derivates (**1–2**, **14–17**) and tetrazines (**18** and **19**).

Entry	Products	Temperature (°C)	Time (h)	Yields (%)
1	**28**; G = H, R = CO_2Me	r.t	12	95[a]
2	**29**; G = Me, R = CO_2Me	r.t	12	95[a]
3	**30**; G = Propargyl, R: CO_2Me	r.t	12	90[a]
4	**31**; G = Carboxamide [–C(=O)NH_2], R = CO_2Me	r.t	12	90[a]
5	**32**; G = H, R = 2-Py	r.t	12	50[a]
6	**33**; G = Me, R: 2-Py	r.t	12	65[a]
7	**34**; G = Propargyl, R = 2-Py	r.t	12	95[a]
8	**35**; G = Carboxamide [-C(=O)NH_2], R = 2-Py	r.t	12	85[a]
9	**36**; G = Ac, R = CO_2Me	130	12	50[b]
10	**37**; G= *N,N*-dimethylsulfamoyl, R = CO_2Me	180	24	15[b]
11	**38**; G = Ac, R = 2-Py	140	15	50[b]
12	**39**; G= *N,N*-dimethylsulfamoyl, R = 2-Py	180	96	35[b]

[a]All reactions were carried out in dry CH_2Cl_2 at r.t. under N_2 atm.
[b]All reactions were carried out in a sealed tube in toluene (see the experimental section for details).



16, G= Ac
17, G= *N,N*-dimethyl-sulfamoyl

18, R= CO_2Me
19, R= 2-Py

36, G= Ac, R= CO_2Me
37, G= *N,N*-dimethylsulfamoyl, R= CO_2Me
38, G= Ac, R= 2-Py
39, G= *N,N*-dimethylsulfamoyl, R= 2-Py

40, R= CO_2Me
41, R= 2-Py

Scheme 3. Synthetic route of *N*-substituted dibenzoazepine-pyridazine derivatives **36–39**.

dienophile *N*-substituted dibenzoazepine derivatives **1–2** and **4–15** with tetrazines **18–19** (Scheme 2). These reactions took place under milder conditions and no oxidation product was formed as a result of the reaction. Therefore, the PIFA was used as an oxidizing agent to access targeted products **28–35** (Scheme 2, Table 1).

The reaction of *N*-substituted dibenzoazepine derivatives **16–17** containing EWGs under similar conditions with tetrazines **18–19** progressed more slowly and a higher reaction temperature was required to carry out the aimed transformation (Scheme 3). Interestingly, the direct oxidation products **36–39** were obtained by changing the reaction conditions, i.e. increasing the temperature and extending the reaction time. When the reaction was performed under a higher reaction temperature in a sealed tube in dry toluene at 110–150 °C for 12–24 h, the formation of dihydrotetrazines **40–41** along with **36–39** was observed (Scheme 3). Since tetrazines **18–19** behaves as an oxidizing agent at the same time, using 1.1 equiv. of **18–19** with **16–17** for 3 days led to the formation of **36–39** and **40–41**.[24,25] The chemical structures of all *N*-substituted dibenzoazepine–pyridazine derivatives synthesized in this study were determined by NMR, IR, and HRMS analyses.

Conclusion

In conclusion, we designed and synthesized novel 12 heterocyclic compounds **28–35** and **36–39** which contain the two important scaffolds for drug discovery, namely

dibenzoazepine and pyridazine heterocycles. This new heterocyclic hybride skeleton may be applicants for the development of neurologically active drug agents. Further studies along this line are underway in our group on the evaluation of pharmacological activity of the aforementioned heterocyclic compounds. The newly synthesized compounds may be interesting with their potential pharmacological and biological activities.

Experimental section

General

All reactions were carried out under nitrogen and monitored by thin-layer chromatography (TLC). All solvents were dried and distilled before use. Column chromatography was performed on silica gel (60 mesh, Merck, Kenilworth, NJ, USA). TLC was carried out on silica gel 60 HF254 aluminum plates (Fluka, Buchs, Switzerland). Melting points are uncorrected. The one- and two-dimensional ^{1}H and ^{13}C NMR spectra were recorded on a Varian-400 or a Bruker-400 spectrometer using tetramethylsilane as the internal reference. All spectra were recorded at 25 °C and coupling constants (J values) are given in Hz. Chemical shifts are given in parts per million (ppm). Mass spectra were recorded on an Agilent Technologies 6530 Accurate-Mass Q-TOF-LC/MS (Agilent Technologies, Santa Clara, CA, USA). IR spectra were recorded on Perkin Elmer FT-IR spectrometer (PerkinElmer, Waltham, MA, USA).

Synthesis

General procedure A: Reaction of N-substituted dibenzoazepine derivatives 1–2, 4–15 with tetrazines 18–19 (Step I): oxidation of obtained the products with PIFA (Step II)

Step I: *N*-substituted dibenzoazepine derivatives **1–2** or **14–15** (1.000 mmol) and tetrazines **18–19** (1.100 mmol) were dissolved in toluene in a sealed tube and the resulting reaction mixture was heated at the required temperature. The reaction was monitored by TLC. The resulting reaction mixture was then cooled to r.t and the solid precipitated to the bottom of the thermolysis tube was washed with a 10 mL ether/*n*-hexane (4:1) mixture and dried under reduced pressure. The crude product was directly used in the oxidation step with PIFA without purification.

Step II: In this step, the cycloadducts **20–27** (1.000 mmol) and PIFA (1.200 mmol) were dissolved in dry CH_2Cl_2 at r.t. under N_2 atm. The resulting reaction mixture was stirred at r.t. for 12 h. The reaction was monitored by TLC and the solvent was removed under reduced pressure. The crudes were purified an appropriate method described in Supporting Information.

General procedure B: Reaction of N-substituted dibenzoazepine derivatives 16–17 with tetrazines 18–19 and to yield diazin-dibenzoazepine derivates 36–39

N-Substituted dibenzoazepine derivatives **16–17** (1.000 mmol) and tetrazines **18–19** (1.100 mmol) were dissolved in solvent toluene in a sealed tube and the resulting

reaction mixture was heated at the required temperature. The reaction was monitored by TLC. The resulting reaction mixture was then cooled to r.t. and the solvent was removed under reduced pressure. The crude was purified an appropriate method described in Supporting Information.

Full experimental details, ^{1}H NMR, ^{13}C NMR, and HRMS spectra can be found via the "Supplementary Content" section of this article's webpage.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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