The 2,6-Xylyl Moiety as a Privileged Scaffold of Pharmaceutical Significance

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The 2,6-xylyl moiety is an attractive scaffold extensively used in the field of medicinal chemistry. The local anesthetic (LA) Lidocaine (or lignocaine, Xylocaine®, Tab. 1) was discovered in 1943, and originally labelled as LL30. Thanks to the presence of the 2,6-xylyl moiety, unlike its congeners, it overcame the systemic toxicity of Tetracaine and Cocaine and had a longer duration of action than Procaine. "Xylocaine® has, for more than three decades, stood the test as a reliable and highly efficient local anesthetic" [1]. Some constrained analogues, bearing a pipecolylxylidide moiety, were then studied: Mepivacaine was introduced in the 1950s, followed by Bupivacaine, in 1965, that gained popularity because of its long duration of action. The closely related compound Ropivacaine was evaluated in clinical trials starting in 1990 and introduced in clinics in 1996. It was less neurotoxic and cardiotoxic than Bupivacaine [2,3]. Pyrrocaine is a LA drug bearing a pyrrolidine moiety used as the hydrochloride salt [4]. Etidocaine is a long-lasting LA used in gynecology and obstetrics, which alleged toxicity has restricted its clinical use. Recently, ionic gradient liposomes have been proposed to increase the upload and prolong the drug release, from liposomes [5]. Interestingly, the use of LAs during clinical cancer surgeries has suggested their potential role in cancer [6], to be used not as stand-alone anticancer drugs but preferably as chemotherapy synergists [7]. Specifically, Lidocaine showed antiproliferative effects *in vitro* on different types of cancer cells (breast, colon, tongue or melanoma) [8]: it selectively inhibits colon cancer cells proliferation without affecting tumor microenvironment (cancer-associated fibroblasts) [9,10]. Thus, its repositioning to anticancer has been proposed [11]. Recent studies on LAs metabolism and toxicity have been reported, also focusing on interaction with other drugs and food [12-19]. Mexiletine and tocainide (Fig. 2) are 2,6-xylyl-substituted derivatives belonging to IB class antiarrhythmic drugs. Their antiarrhythmic activity is due to the block of human cardiac voltage gated

sodium channels, namely hNav1.5 [20,21]. Moreover, as blockers of voltage-gated Na^+ channels, they have been extensively studied for their antimyotonic activity [22,23], acting on human skeletal muscle voltage gated sodium channels (hNav1.4), and for the activity in neuropathic pain, exerted by blocking hNav1.7 and hNav1.8 channels, which are sodium channel subtypes predominantly expressed in peripheral nociceptive neurons [24]. Several analogues of these compounds, even more active than the parent compound, were described in the literature, both in their racemic and/or optically active forms [25-28]. The deuterated phenyl analogue of mexiletine, bearing the 2,6-xylyl portion, has been recently reported: it shows superior cardiovascular, metabolic and pharmacokinetic properties, and improved safety profiles [29]. Moreover, several metabolites of mexiletine have been studied for their antiarrhythmic and/or antimyotonic properties [30,31]. Interestingly, the metabolite *m*-hydroxymexiletine (MHM) was 2-fold more potent than the parent compound on the cardiac sodium channels showing more favorable toxicological properties than mexiletine since it did not impair motor coordination in contrast to mexiletine and showed no cytotoxicity on human hepatocellular liver carcinoma (HepG2) cells [32,33]. Lidoflazine is an old atypical calcium channel modulator as it is defined a non-dihydropyridine; it has been recently reconsidered [34,35]. Ranolazine (Ranexa™) is a drug approved by Food and Drug Administration (FDA) in 2006 for the treatment of chronic stable angina pectoris and as an antiarrhythmic [36]. This property is exerted by blocking late sodium currents over peak fast sodium currents. Ranolazine has also demonstrated hypoglycemic properties in pre-clinical and clinical studies, through the inhibition of glucagon secretion from pancreatic islets, as it blocks sodium channels (Nav1.3 isoform) in α-cells. It has been recently demonstrated also to be effective against cognitive impairment and depressive-like behavior [37]. Lidamidine is a derivative of guanylurea, which is a drug used to treat diarrhea, by affecting peripheral alpha-2 adrenoceptors [38]; it can also show anticoagulant and analgesic effects [39]. Lopinavir (ABT-678) is an extremely potent inhibitor of HIV-1 protease (K_i = 1.3 pM) that was licensed in combination with ritonavir (as Kaletra™, Abbott Laboratories) for anti-retroviral therapy in 2000 [40]. Its metabolism and doses are currently under study for the emerging Coronavirus

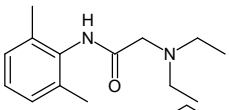
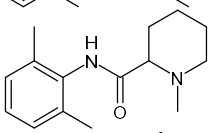
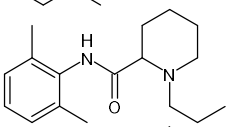
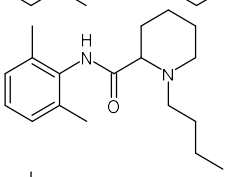
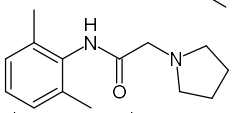
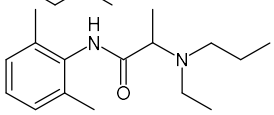
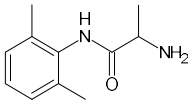
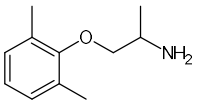
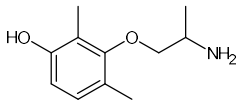
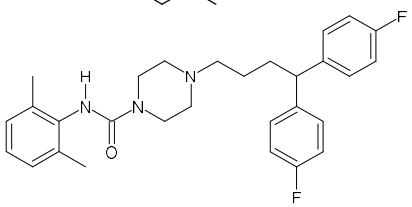
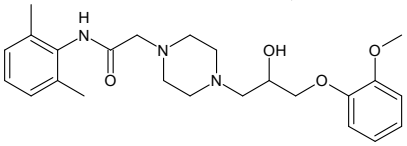
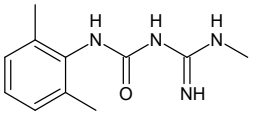
Disease 2019 (COVID-19), in association with the antiviral ritonavir [41,42]. Xylazine is a novel adulterant with fentanyl in fatal drug intoxications, which has public health, safety, and criminal investigative implications. It is a non-narcotic sedative used for analgesia and muscle relaxation uniquely in veterinary medicine [43].

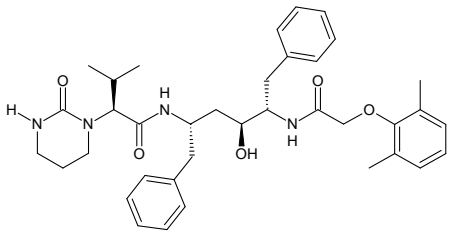
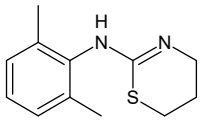
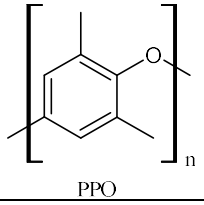
The 2,6-xylyl moiety also characterize new synthetic compounds studied in the literature for antimicrobial activities. A 2,6-xylyl derivative was used to determine the X-ray crystal structure of bacterial *Enterococcus faecalis* thymidylate synthase (*Ef*TS) [44,45]. Recently, antimicrobial activity was found for several analogues of triclocarban, a chlorinated highly effective and broad-spectrum antimicrobial and antiseptic agent that is often found in personal care products, despite its toxicity [46]. The new compounds belong to the class of diarylureas [47], known anticancer agents recently proposed for repositioning to antimicrobial agents [48]. Among the studied compounds, the most interesting were those bearing the 2,6-xylyl moiety: they were more active than triclocarban and, unlike triclocarban, they were not cytotoxic against the human mammary epithelial and embryonic kidney epithelial cells [49,50].

Finally, the 2,6-xylyl moiety is worthy of note in materials chemistry. Poly(2,6-dimethyl-1,4-phenylene)oxide (PPO) is a widespread high-performance commercially available polymer, being generally amorphous and exhibiting a high glass-transition temperature ($T_g \approx 220$ °C), which has been identified as a valid membrane material, used since ancient times [51]. Quaternized PPO copolymers have been recently described as anion exchange membranes for alkaline fuel cell application [52].

In conclusion, the 2,6-xylyl moiety may be considered an interesting and important scaffold in medicinal and materials chemistry. In the presence of this moiety, various pharmacological activities have been found, obtaining compounds that are also generally devoid of cytotoxicity.

Table 1. Structures and activities of compounds bearing the 2,6-xylyl moiety described in the text

Structure	Name	*Activity* [Ref]	Toxicity [Ref]
	Lidocaine	*LA* [1,12]	[8,11,53-55]
	Mepivacaine	*LA* [2,12]	[2]
	Ropivacaine	*LA* [3,12]	[8,55]
	Bupivacaine	*LA* [3]	[8,55]
	Pyrrocaine	*LA* [4,12]	[58]
	Etidocaine	*LA* [5]	[5]
	Tocainide	*Antiarrhythmic* [21] *Antimyotonic* [23,26] *Action in neuropathic pain* [21]	[59]
	Mexiletine	*Antiarrhythmic* [28,32] *Antimyotonic* [56] *Action in neuropathic pain* [57]	[28,32]
	MHM	*Antiarrhythmic* [32] *Antimyotonic* [56]	[32]
	Lidoflazine	*Antiarrhythmic* [35]	[60]
	Ranolazine	*Treatment of chronic stable angina pectoris* [36,37]	[61]
	Lidamidine	*Antidiarrheal* [38]	[62]

	Lopinavir	*HIV-1 protease inhibitor* [42]	[42]
	Xylazine	*Veterinary non-narcotic sedative* [43]	[63]
 PPO	PPO	*Materials Chemistry* [51,52]	

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